

Review

Open Access

Computational models in plant-pathogen interactions: the case of *Phytophthora infestans*

Andrés Pinzón*^{1,2}, Emiliano Barreto², Adriana Bernal¹, Luke Achenie³,
Andres F González Barrios⁴, Raúl Isea⁵ and Silvia Restrepo¹

Address: ¹Mycology and Phytopathology Laboratory, Department of Biological Sciences, Universidad de los Andes, Bogotá, Colombia, ²Bioinformatics center, Colombian EMBnet node, Biotechnology Institute, National University of Colombia, Bogotá, Colombia, ³Department of Chemical Engineering, Virginia Polytechnic Institute and State University, Blacksburg Virginia, USA, ⁴Grupo de Diseño de Productos y Procesos, Department of Chemical Engineering, Los Andes University, Bogotá, Colombia and ⁵Fundación IDEA, Centro de Biociencias, Hoyo de la puerta, Baruta 1080, Venezuela

Email: Andrés Pinzón* - am.pinzon196@uniandes.edu.co; Emiliano Barreto - ebarretoh@unal.edu.co; Adriana Bernal - abernal@uniandes.edu.co; Luke Achenie - achenie@vt.edu; Andres F González Barrios - andgonza@uniandes.edu.co; Raúl Isea - risea@idea.gob.ve; Silvia Restrepo - srestrep@uniandes.edu.co

* Corresponding author

Published: 12 November 2009

Received: 30 April 2009

Theoretical Biology and Medical Modelling 2009, **6**:24 doi:10.1186/1742-4682-6-24

Accepted: 12 November 2009

This article is available from: <http://www.tbiomed.com/content/6/1/24>

© 2009 Pinzón et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: *Phytophthora infestans* is a devastating oomycete pathogen of potato production worldwide. This review explores the use of computational models for studying the molecular interactions between *P. infestans* and one of its hosts, *Solanum tuberosum*.

Modeling and conclusion: Deterministic logistics models have been widely used to study pathogenicity mechanisms since the early 1950s, and have focused on processes at higher biological resolution levels. In recent years, owing to the availability of high throughput biological data and computational resources, interest in stochastic modeling of plant-pathogen interactions has grown. Stochastic models better reflect the behavior of biological systems. Most modern approaches to plant pathology modeling require molecular kinetics information. Unfortunately, this information is not available for many plant pathogens, including *P. infestans*. Boolean formalism has compensated for the lack of kinetics; this is especially the case where comparative genomics, protein-protein interactions and differential gene expression are the most common data resources.

Background

Control and management of plant diseases and the identification of factors that contribute to the spread a given plant pathogen attack are at the basis of phytopathology. Mathematical models and computational simulations have been used, along with molecular and physiological approaches, to solve these and other issues.

In the early 1990s the use of stochastic models in plant pathology was reviewed [1,2], mostly focused on epidem-

ics. In this work we update topics not fully covered in previous reviews as well as associated experimental approaches that characterize the systems biology era [3]. Most of the review will focus on the *Phytophthora infestans* - *Solanum tuberosum* pathosystem, but its discussion will be general enough as to be applicable to any other plant pathogen system. A brief discussion of boolean networks and how this approach could drive the modeling of the compatible interaction between *P. infestans* and *S. tuberosum* is also introduced.

Experimental approaches to the study of molecular plant-pathogen interactions in *Phytophthora* species

Plants use various strategies to resist infection by a particular pathogen [4]. These strategies are part of the plant's innate immune system and can be grouped into two broad categories [5]. The first recognizes common pathogen-associated molecular patterns (PAMPs), and acts as an early plant warning to potential infection [6]. This recognition leads to the induction of a basal plant defense, which in some cases includes a hypersensitive response (HR). The HR is characterized by the rapid death of cells surrounding the infected region and commonly leads to a broad spectrum plant response, the Systemic Acquired Resistance [7].

A second defense system in plants involves pairs of gene products, an effector molecule from the pathogen and an associated resistance protein (R) from the host, which recognizes it. This defense mechanism is highly specific and is triggered once a given effector is recognized by its associated R defense protein [5].

Plants with the capacity for protection from a pathogen attack are considered as resistant and a pathogen that lacks the ability to infect it is referred to as avirulent on that plant [4]. In this case, the host-pathogen interaction is considered incompatible. On the other hand, when a compatible interaction occurs, the pathogen becomes virulent and a plant that is incapable of resisting the attack is considered non-resistant.

Plant pathogens have developed several strategies to evade such plant defense responses and to become virulent. For some of these pathogens the evasion mechanisms are at least partially known, as in the case of bacteria such as *Pseudomonas syringae*. However, for most plant pathogen species, these evasion mechanisms are almost completely unknown. This is the case for *P. infestans*, the causal agent of late blight of potato, a disease that affects *S. tuberosum* and some other species in the *Solanaceae* family [8]. Oomycetes from the genus *Phytophthora* are plant pathogens devastating for agriculture and natural ecosystems [9]. For instance, in the United States alone, *P. infestans* causes estimated losses that exceed \$US 5 billion annually [10].

Despite its economic importance, the fundamental molecular mechanisms underlying the pathogenicity of *P. infestans* are poorly understood. It was not until recent years that information crucial to the understanding of its genomics and infectious mechanisms was accessible to the research community [11]. For example, in 2006, the first effort to classify the secretome of plant pathogenic Oomycetes was carried out by Kamoun et al. Furthermore, although the general molecular events associated with the

interaction between *P. infestans* and *S. tuberosum* were already known in 1991 [12], it was not until last year (2008) that all the known molecular and cytological processes underlying plant-pathogen interactions in various *Phytophthora* species were revised [9].

From the biological strategies used so far to study the processes underlying plant-pathogen interactions, three are most suitable as basis for a computational systems biology approach: (a) gene expression, (b) structural and comparative genomics and (c) protein-protein interactions.

Gene expression

Gene expression approaches constitute a starting point from which to determine the best strategy for building a computational model of a plant disease. Host-expressed molecules give insights into the underlying defense mechanisms, whereas identification of the pathogen counterparts allows us to ascertain possible mechanisms of attack and/or avoidance mechanisms used to establish a disease.

Differential expression of particular genes

A common strategy in gene expression analysis is to identify a particular gene of interest, and then to study or characterize its expression profile in different hosts and/or treated tissues. For instance, based on the findings that during the early phases of the interaction between *P. infestans* and potato, the genes *ipiB* and *ipiO* are expressed at high levels, Pieterse et al. hypothesized that these genes played an important role in the early stages of the infection process [13]. Both genes were isolated and their expression studied in various host tissues and different host plants. The results showed that the expression of these genes was activated in compatible, incompatible and non-host interactions. In the case of *ipiO*, it was revealed that a motif on the promoter region functioned as a glucose repression element in yeast. This observation helped to generate hypotheses about its behavior in cultivars with different resistance levels. The authors concluded that perhaps a variable nutrient environment could trigger the expression of *ipiO* and *ipiB* depending on the host and/or the expressing tissue.

Most of the crucial *P. infestans* protein elicitors known to date [14] have also been revealed by this approach. This is the case for the *Avr3a* avirulence gene, the first to be cloned from *P. infestans*. Subsequently, this gene was the subject of the first report of cell death suppression from a filamentous plant pathogen [15,16].

Differential expression of particular genes has also been used to study Systemic Acquired Resistance (SAR) and HR in challenged plants [17,18] to test, for instance, the cor-

relation between the expression of basal SAR marker genes with resistance to *P. infestans* [19].

High throughput differential gene expression

This approach focuses in the identification of all the genes expressed in a cell under a particular condition. Since this approach allows us to differentiate clearly between the expression profiles of cells under different conditions, its application is of special interest in plant-pathogen interactions, allowing us to solve research questions such as: which genes are expressed in a compatible interaction that are not expressed in a incompatible one? Or, are there any sub-regulations, positive or negative feed-backs, present in one case but not the other?

Different techniques such as DNA microarrays [20-23], serial analysis of gene expression [24,25] and differential display [26,27] have been used to study high throughput differential gene expression.

In the case of *P. infestans*, genes expressed in host cells challenged by this pathogen have been screened on compatible [28-30] and incompatible interactions [31-33], elucidating important issues about the mechanisms of interaction with its hosts.

For instance, gene regulation was revealed in a DNA microarray analysis of 7680 potato cDNA clones, representing approximately 5000 unique sequences expressed during a compatible interaction [30]. This work focused on the role of gene suppression in the compatible interaction, and its profile was obtained from microarray data evaluated at five time points. From this study, suppression of genes involved in the jasmonic acid (JA) defense pathway was revealed [34], as well as a severe down-regulation of the carbonic anhydrase (CA) gene, responsible for the reversible hydration of carbon dioxide to bicarbonate. Further analysis showed that CA was first down-regulated and then up-regulated during the incompatible interaction, clearly differentiating susceptibility from resistance, opening questions about the mechanisms that lead to its rapid suppression and the possibility of a connection between CA suppression and the overall down-regulation of the JA defense pathway.

Differential expression has also been studied on the pathogen side in *P. infestans* [35,21,23] and other *Phytophthora* species [21,36], revealing differential expression of e.g. the hsp70 and hsp90 genes, under distinct pathogen developmental stages and pathogenicity structures [37,36].

Although still fragmented, this approach provides a systemic view of the pathogenicity process, considering gene expression as a network and helping us to develop strate-

gies to control or prevent the disease by manipulation of either the pathogen or the host.

Structural and comparative genomics

Along with differential gene expression analysis, this is the most common modern approach to studying plant pathogen interactions, mostly due to the proteomic techniques as well as data mining and functional genomics tools available nowadays.

To date, one nuclear and six chloroplast genomes have been sequenced and two more nuclear genome sequencing projects are in progress in *Solanaceous* species (Additional file 1). On the pathogen side, five Oomycete genomes have been sequenced [11] and several studies at the genome scale have been carried out thanks to the availability of genomic information on these Oomycetes [38-40] and their hosts.

Therefore, the possibility of performing comparisons between different organisms at the sequence level [40] has allowed agronomically important resistance genes in potato to be isolated [41], pathogen avirulence genes [42] and gene families [10] to be identified, and novel proteins implicated in a given interaction to be identified [43]. For example, in the case of *S. tuberosum*, comparative analysis has revealed a physical co-localization between resistance loci in tomato, tobacco and pepper [44].

This approach has also revealed how two widely divergent microorganisms, *P. infestans* and the human malaria parasite *Plasmodium falciparum*, use equivalent host-targeting signals to deliver virulence and avirulence gene products into their hosts [45]. These products have been characterized by a particular protein motif, leading to the hypothesis of pathogenicity mechanisms conserved between both organisms [46]. This motif is the host-targeting (HT) signal of *P. falciparum*, centered on an RxLx core, revealed after the discovery of the RxLR host translocation motif of Oomycete effectors [47-49]. Owing to the availability of such data, it has been shown that although *Plasmodium* and *Phytophthora* are divergent eukaryotes, they share leader sequences, which suggests a conserved machinery for transport of effector proteins, a finding otherwise hard to achieve.

Protein-protein interactions

One approach to study protein-protein interactions is by using yeast two hybrid screening, co-immunoprecipitation [50] or surface plasmon resonance. This is arguably the most important approach towards a broad understanding of any plant pathogen interaction. It enables some mechanisms for the suppression of host defense in several organisms, such as the fungal pathogen *Septoria*

lycopersici [51] or the Oomycete *Phytophthora sojae* [52], to be revealed.

In the case of *P. infestans*, relevant host defense suppression molecules have been also identified by this approach, such as the extracellular protease inhibitors *EPI1* [53], *EPI10* - the first protease inhibitor reported in any plant-associated pathogen, which suppresses tomato defense by targeting - the *P69B* subtilisin-like serine protease [54], and the *EPIC* family of secreted proteins that target the extracellular cysteine protease PIP1 (*Phytophthora* Inhibited Protease 1) [55].

Protein-protein interactions play an important role in recognition between plant pathogens and their hosts. This recognition has been studied at two levels: recognition of the host by the pathogen and recognition of the pathogen by the host [56,57]. During an interaction, host resistance (*R*) and pathogen avirulence (*Avr*) proteins interact in a gene-for-gene manner. Proteins encoded by *R* alleles recognize the products of corresponding *Avr* alleles, thus triggering disease resistance. Using an association genetics approach [58], the *P. infestans Avr3a* effector was shown to be recognized in tomato cytoplasm by *R3a* (a member of the *R3* complex locus on chromosome 11). *R3a* was isolated by positional cloning the same year [41].

Together, these and other studies [59,23], along with computational chemistry and/or computational modeling and prediction of protein-protein interactions [60], provide valuable information about the recognition mechanisms in *S. tuberosum* - *P. infestans* *R-Avr* interactions and could lead to the identification of metabolic and/or signaling pathways underlying incompatible interactions.

Quantitative models in plant pathology

In cases where experimental data for a biological system start to accumulate, it is feasible and convenient to integrate all the information gathered into a quantitative model. This approach allows us to obtain a mathematical and networked framework for a descriptive model of the biological phenomenon [61]. This type of model strengthens the predictive capacity of future responses, for instance under different conditions, and it also helps to broaden our view of the potential interactions that could take place in any molecular reaction [62].

In order to capture time-dependent dynamic phenomena, a systems biology approach should allow us to integrate various ranges of spatial and temporal biological scales, as well as processing of different signals, genotypic variation and responses to external perturbations. As seen in the previous section, typical experiments describing the inter-

action between *P. infestans* and its hosts are clearly related to each of these characteristics.

Functional genomics and proteomic approaches produce the most suitable data for the development of a theoretical model [61]. For instance, microarray-based differential expression analysis evaluates expression patterns at different times [30], under different conditions [21,33] with host and pathogen genotypic variation. On the other hand, gene expression and host targeting of protease inhibitors work at different levels of signaling and at different spatial and temporal scales [54,53].

Data gathered from such plant-pathogen interaction approaches, along with the development of interaction, pathways and metabolism databases [63,64], as well as standardized systems biology languages [65,66] and *in silico* research platforms [67,68], have opened the door to modern computational model approaches at the molecular level in several organisms, including Oomycetes.

Predominantly, phytopathologists have used computational and quantitative modeling approaches to describe the temporal dynamics of plant diseases. Consistently, the bulk of the literature written in this field has been focused on the epidemiology of the disease, so research on the modeling of plant-pathogen molecular interactions is under-represented.

Quantitative modeling of plant-pathogen epidemiology

Deterministic approaches

In 1969, Waggoner and Horsfall published Epidem, the first computer simulation of a plant disease [69]. Epidem was mainly a simulator of potato and tomato blights. Since then, models used in the plant-pathogen field have often belonged to the family of logistic equations.

The fundamental logistic model was proposed in 1963 by VanderPlank [70,71] and it describes the rate at which a disease spreads over time (Table 1).

Table 1: Solanaceous genome projects.

Species	Genome	Status	reference
<i>Nicotianatabacum</i>	mitochondrion	Finished	[106]
<i>Nicotianatomentosiformis</i>	chloroplast	Finished	[107]
<i>Solanum tuberosum</i>	chloroplast	Finished	[108]
<i>Solanum bulbocastanum</i>	chloroplast	Finished	[109]
<i>Solanum lycopersicum</i>	chloroplast	Finished	[110]
<i>Nicotianasyvestris</i>	chloroplast	Finished	[111]
<i>Atropa belladonna</i>	chloroplast	Finished	[112]
<i>Solanum tuberosum</i>	Nuclear	In progress	12984*
<i>Solanum lycopersicum</i>	Nuclear	In progress	9509*

*NCBI's genome project identification number.

In this model [71], γ_t is the proportion of diseased tissue (severity) at time t and λ is the rate of change of diseased tissue unit in a given unit time. The term $(1-\gamma_t)$ indicates that new infections occur only in non-infected tissue. The slope of the disease curve depends on the infection rate (λ) and the inoculum γ_t . At a higher infection rate, the curve rise more steeply.

However, this model assumes that a lesion always remains infectious and also neglects the lag between the time at which an infection occurs and the time it becomes infectious (latent period). As such, the so-called generalized model considers both a latent period ($p > 0$) and an infectious period (i) [71,72] (Table 1). These values can range from $p < 7$, $i < 65$ days in *Puccinia recondita* [73] to $p < 2$, $i < 8$ days in *P. infestans* [74].

Other relevant characteristics of a plant disease are its spatial pattern and the arrangement of disease entities (i.e., spores). The spatial patterns are influenced by dispersal of disease entities [75]. In cases where spore dispersal is not carried out directly from infected tissue but by environmental factors such as wind, a model assuming a constant source of inoculum, such as a monomolecular model, is more appropriate [71].

In this case the infected tissue is not part of the source, so the shape of the disease curve depends solely on the rate of infection. In the case of *Phytophthora*, five potential mechanisms of dispersal have been described for some major species [75]; for *P. infestans*, *P. cinnamomi* and *P. syringae*, a real mechanism of dispersal could be represented correctly by this model.

Some other models have been derived from the general logistic model. For instance, the Gompertz model is similar to the general logistic one and can be seen as a logarithmic form of it. When different data sets are compared, it is appropriate to use a model that allows us to make such comparisons; for those cases a Weibull model should be considered [76].

The spread of disease has also been modeled [77,78]. Since the early 1980s, the epidemic wave velocity of *P. infestans* has been measured by several means [79-82].

Although widely used, deterministic models do not represent the underlying biological process in a proper way. Spore germination is a good example of a stochastic process; for instance, examination of a single spore will reveal stochastic behavior, which can only be inferred by the examination of a significant number of units. Thus, in these cases, the process under study is better described by a probability function [2].

Stochastic approaches

Stochastic modeling of epidemics has been studied since the early 1960s. Most of the stochastic approaches carried out at that time were also concerned with the progress of the infection over time, represented by the so-called general stochastic epidemic model [83]:

$$\Pr\{I(\tau + \delta) = \chi + 1, S(\tau + \delta_\tau) = \gamma - 1 \mid I(\tau) = \chi, S(\tau) = \gamma\} = \beta_{\chi\gamma} \delta_\tau + \varphi(\delta_\tau)$$

Where $(\tau, \tau + \delta_\tau)$ is the time interval. Here $I(\tau)$ represents the number of infectives, $S(\tau)$ the number of susceptibles and $R(\tau)$ the number of removals at time $\tau \geq 0$. The removal of infected tissue is also considered probabilistic and it will occur with the following probability [83]:

$$\Pr\{I(\tau + \delta) = \chi - 1, S(\tau + \delta_\tau) = \gamma \mid I(\tau) = \chi, S(\tau) = \gamma\} = \gamma_{\chi\gamma} \delta_\tau + \varphi(\delta_\tau)$$

in the same time interval, where $\gamma > 0$; $\chi = 0, 1, \dots, N$. Since a given removal does not depend on previous ones, a removal is considered independent [83]:

$$\Pr\{I(\tau + \delta) = \chi, S(\tau + \delta_\tau) = \gamma \mid I(\tau) = \chi, S(\tau) = \gamma\} = 1 - \gamma_{\chi\gamma} \delta_\tau - \beta_{\chi\gamma} \delta_\tau + \varphi(\delta_\tau)$$

Transition probabilities are given as [83]:

$$P_{\chi\gamma}(\tau) = \Pr\{I(\tau) = \chi, S(\tau) = \gamma \mid I(0) = i, S(0) = s = N - i\}$$

In non-stochastic models, stochasticity can be approached by adding randomness to state variables. For instance, Vanderplank's model was used in the description of the zucchini yellow mosaic virus disease [84]. In this case, stochasticity was achieved by adding a "brownian motion term to the growth rate parameter". As the authors stated, a significant difference between a stochastic and a deterministic version of the same model can be seen only if large data sets are employed. This observation could explain why in recent years, when biological data acquisition has grown faster than ever, the use of stochastic models has become more popular.

Stochastic modeling in plant pathology has also been applied to processes at different levels of biological organization, such as at the organ level, crops [85], spatial patterns, evolution [2] and aerial spread [86]. For instance, the spatial spread of disease in race-specific and race-non-specific cultivar mixtures was studied using a *spatially explicit stochastic model* [87]. This model was based on the assumption that disease can be significantly higher in monocultures than in cultivar mixtures and it only considered stochastic variation of spore dispersal at constant sporulation rate, although there exist many other sources of stochastic variation (such as genotypic variation) [2].

No matter whether they are stochastic or deterministic, the models described above have been focused on higher

scales of plant pathogen interactions, such as the population, organ or ecological level. Nevertheless, in any plant-pathogen disease, the molecular level of the interaction (i.e., protein-protein, protein-DNA, regulatory and metabolic network regulation) is intrinsically involved and surely accounts for much of the variation observed at other levels. Therefore, genetic processes in an organism can be seen as networks that *bridge the gap between genotype and phenotype* [88]. A good example of this situation can be found in the collective behavior of bacteria in Quorum Sensing (QS) mechanisms.

QS is a common strategy used by several plant-pathogenic bacteria to assess local population density and/or physical confinement. In a recent publication, a model describing the Ti plasmid quorum-sensing gene network was constructed [89]. It was shown that it could operate as an "on-off" gene expression switch that is sensitive to the environment, allowing the question about how bacteria really behave or respond to be answered in QS.

Although this topic is absent in some plant-pathogen organisms, such as *P. infestans*, the characteristics of quantitative modeling of molecular mechanisms could elucidate several questions in phytopathology.

In silico modeling of plant-pathogen molecular interactions

Plants resist pathogen attacks by shifting their defense mechanisms, as reflected in quantitative and kinetics enhancements [62]. The mechanism that controls host defense activation consists of a highly interconnected network, in which host defense genes interact with each other as well as with effector proteins present in the cell [90-92]. The availability of high-throughput gene expression and proteomics data has generated an unprecedented opportunity for comprehensive study of these types of biological networks [89,93].

Since an important phase in host-pathogen interactions involves protein-protein recognition [94,91], efforts to elucidate networks of such interactions are of special interest in phytopathology. For example, a whole-genome computational strategy to infer protein interactions was applied to ten pathogens, including species of *Mycobacterium*, *Apicomplexa* and *Kinetoplastida* [91]. This work started with the identification of pairs of matching proteins known to interact between the host and the pathogen, and by assessing the likelihood of this interaction by means of structural modeling, expression properties and subcellular location. As a result, an enriched candidate set of proteins is obtained, suitable for experimental study.

With the current genome sequence information for several *Phytophthora* genomes (Additional file 1) and those

under sequencing [11,95], this approach could be applicable to a *Phytophthora-Solanaceae* model and thus enhance our limited knowledge about the molecular interactions in these genera.

Another good theoretical framework to start working with is a *space of interconnected operators* such as a boolean network (Figure 1). Boolean networks present some advantages when compared to similar strategies such as hidden Markov models [96,97]. For instance, it is possible to perform a simulation while "avoiding the statistical basis around them, provides the option to perform simpler computational simulations, insert additional regulators or quantitative and biochemical data parameters into the model when available" [98].

Towards a boolean description of the *P. infestans* - *Solanum tuberosum* interaction

Although clustering analysis can be used to infer gene function from expression data, the detailed interaction between genes within or between clusters cannot be deduced by this approach [99]. In order to deduce such interactions, data from differential expression analysis can be represented in a boolean formalism. This representation can be achieved in a typical boolean binary form, where repression and/or induction of a given gene can be expressed by an *on* or *off* switch and thus translated into a network structure and simulated by computational analysis. This approach has been successfully implemented in the simulation of plant defense signaling networks in *Arabidopsis thaliana* in response to different treatments with

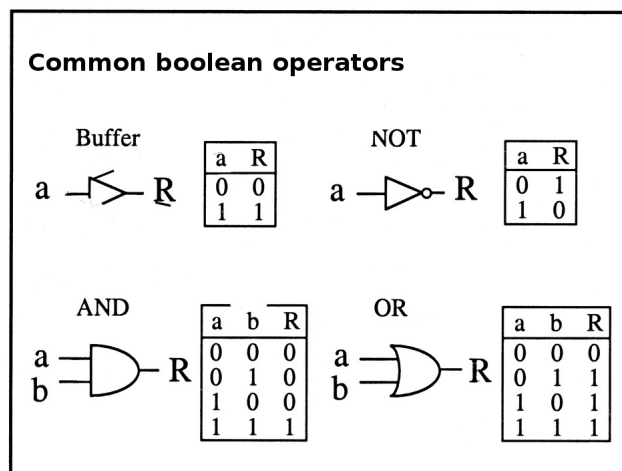


Figure 1
Boolean formalism. Adapted from [98] The most frequent types of boolean operators are the buffer, NOT, AND and OR gates. Tables adjacent to each of these gates are known as "true" tables, where "a" and "b" represent the input (or stimuli) and R the output (or response).

salicylic acid, jasmonic acid and ethylene [98] (figure 2). For example, genes up-regulated to the same level in both treatments can be expressed by an OR operator, as in the case of *PhyA* and *PhyB* in figure 2, thus leading to different possible initial states (input domains) as represented by panels A and B in the same figure. Data from differential expression analysis can also be represented by three possible boolean states (Table 2). This approach has been successfully used in the inference of gene regulatory networks [100] where "-1" was also introduced to address the negative interaction between components in the network. Experimental information on the compatible interaction between *P. infestans* and *S. tuberosum* is being approached by our laboratory using a similar strategy, in order to hypothesize the network space of carbonic anhydrase in this interaction.

This approach can also be used in systems lacking biological information, by gathering data common to other organisms or from related species. This possibility opens the door to implementation in other species of Oomycetes where lack of information is typical.

Conclusion

The idea of the stochastic modeling of biological systems is not new, although traditionally, the mathematical frameworks used to represent and study these processes have been deterministic. This situation can be explained by taking into consideration the fact that quantitative and computational modeling usually require the availability of important computational resources. These resources increase proportionally with the number of variables involved in the model; then apart from restrictions on the

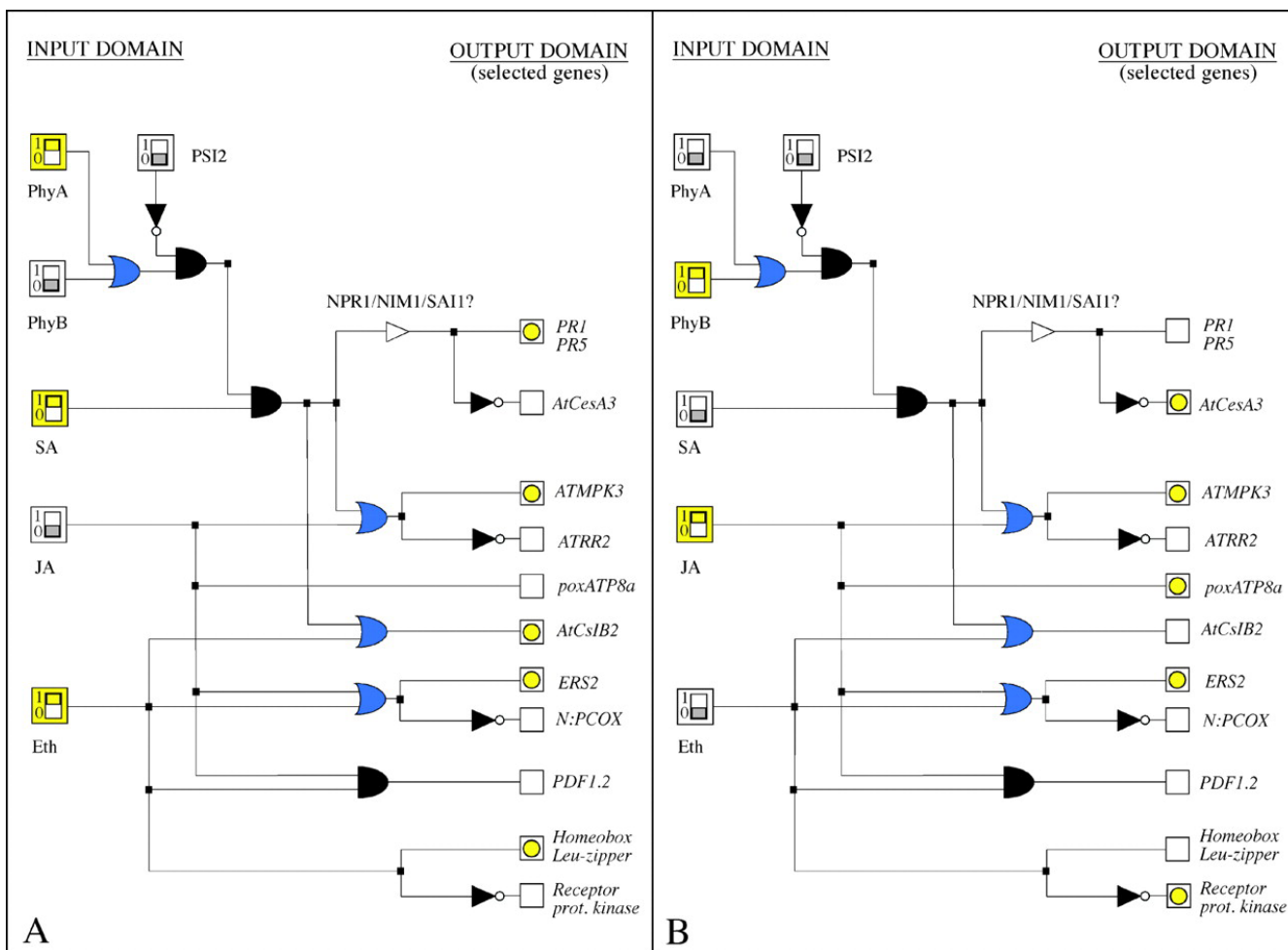


Figure 2
Boolean representation of a signaling network. Adapted from [98] Boolean representation of the signal transduction network controlling the plant's defense response against pathogens in *Arabidopsis thaliana*, represented by a series of output genes selected from microarray data. The activated switches are represented in yellow. Diode symbols in yellow indicate the induced genes. Empty squares correspond to no significant expression. A and B represent two of the various possible outputs given the input.

Table 2: Boolean representation of defense-related genes expressed during a compatible interaction between *P. infestans* and *S. tuberosum*.

Gene name	6 h		12 h		24 h		48 h		72 h	
Carbonic anhydrase	0.6	<i>-1</i>	0.6	<i>-1</i>	0.5	<i>-1</i>	0.3	<i>-1</i>	0.3	<i>-1</i>
Proteinase inhibitor II	0.9	0	1.1	0	0.5	<i>-1</i>	0.5	<i>-1</i>	0.4	<i>-1</i>
Peroxiredoxin	1.0	0	0.8	0	0.7	<i>-1</i>	0.7	<i>-1</i>	0.7	<i>-1</i>
2-Cys peroxiredoxin	1.0	0	0.9	0	0.6	<i>-1</i>	0.6	<i>-1</i>	0.5	<i>-1</i>
Proteinase inhibitor I	1.0	0	0.9	0	0.6	<i>-1</i>	0.9	0	0.6	0
Superoxide dismutase	0.9	0	0.8	0	0.8	0	0.7	<i>-1</i>	0.7	<i>-1</i>
Peroxidase	0.8	0	0.9	0	0.9	0	0.8	0	0.6	<i>-1</i>
Aspartic proteinase inhibitor	1.7	1	1.0	0	1.2	0	1.1	0	0.7	<i>-1</i>
Cystein proteinase inhibitor	1.5	1	1.9	1	1.1	0	1.2	0	0.6	<i>-1</i>
Cysteine protease	1.0	0	1.4	0	1.3	0	1.4	0	2.0	1
Peroxidase	1.2	0	1.3	0	1.3	0	1.4	0	2.5	1
Catechol oxidase	1.5	1	2.4	1	1.4	0	1.8	1	2.5	1
Catalase	1.4	0	1.7	1	1.9	1	2.3	1	3.3	1
Glutathione reductase	1.8	1	1.8	1	1.6	1	2.3	1	3.0	1

Adapted from [30]. Inductions, quantified as ratios greater than 1.5-fold, are represented in bold font. Repressions, quantified as ratios lower than 1.5-fold, are represented in bold and italic font. Grey columns contain the boolean representation for each gene expression level. Inductions here are represented by 1, repressions by -1 and non-significant expression by zero. These boolean values can further be formalized and simulated into a computational model.

availability of biological information included in the model, there also exist restrictions on the availability of computational resources to perform a given simulation. In recent years, computational resources have become less restrictive. Moreover, stochastic processes are probabilistic in nature and thus require the use of more data as confidence in calculations depends on them. More data means more calculations and interconnections between variables. Thus, the availability of computational resources and biological data has restricted the use of stochastic approaches for decades, not only in plant pathology, but in biological processes in general.

Any top level biological observation implies an underlying molecular process, which is not isolated from its environment. This situation has always been evident to plant pathologists, as reflected in the conversion of environmental factors such water or humidity into model variables. Epidemiological research will find molecular plant-pathogen interaction models an important tool for describing disease spread and dynamics from its roots. In turn, molecular plant pathogen interactions cannot be modeled in isolation from environmental variables, largely analyzed by deterministic approaches since the early 1960s. Therefore, in order to reflect the real biological phenomena, it is crucial to take this information into account when a molecular interaction is considered.

Biological information that implies a networked structure can be represented by a boolean formalism. This approach avoids the immediate necessity of chemical kinetics and the use of sets of equations (for example differential equations) to run a simulation. Thus, boolean

networks are a viable and ideal strategy for the computational modeling of protein-protein interactions, metabolic networks and differential expression data available today for organisms for which molecular kinetic information is not available.

To date, differential gene expression data, protein-protein interaction and functional comparative analysis represent the only information available, not only for the majority of Oomycetes and their hosts but also for several other organisms. Here we argue that, due to the type of information available - although hidden Markov models, neural networks and flux balance analysis have recently been used - a boolean representation of plant-pathogen interactions between *P. infestans* and *S. tuberosum* is one of the most suitable approaches for computational modeling; an ongoing effort in our laboratory, based on microarray data for a compatible interaction between these organisms. Once available, boolean networks will allow kinetic information to be put back into the model and thus complement it with new information as it becomes available.

Quantitative representation and computational simulation of biological data is an important tool for understanding complex biological networks and interactions. To date, the availability of efficient algorithms, biological information and computational resources have opened the door to new insights into the analysis of such information. Bioinformatics, systems biology and its most representative tool, computational modeling, allow us to study complex plant pathogen interactions in a way unreachable to scientists two decades ago. Understanding of plant-pathogen interactions at the deterministic and stochastic,

molecular and population levels requires a holistic approach, where any piece of available information is important. Today we are facing an integrative era of biological information, which approaches biological phenomena not from their individual parts but from their interactions. Without a doubt, this approach reflects biological reality in a more convenient and realistic way, but it also brings new challenges as well as the necessity for new tools, which cover not only the biological sciences field but also engineering and mathematics.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AP and SR conceived the overall direction and major sections of the manuscript. All authors contributed to writing the manuscript.

Additional material

Additional file 1

Fundamental deterministic models used in plant pathology.

Click here for file

[<http://www.biomedcentral.com/content/supplementary/1742-4682-6-24-S1.pdf>]

Acknowledgements

The authors thank the Vicerrectoria de Investigaciones at Los Andes University, Colombia for its support.

References

- Rouse D: **Stochastic modeling of plant disease epidemic processes.** *CSA* 1991, **1**:647-665.
- Shaw M: **Modeling stochastic processes in plant pathology.** *Annual Reviews in Phytopathology* 1994, **32**:523-544.
- Kitano H: **Systems biology: a brief overview.** *Science* 2002, **295**(5560):1662-1664.
- Cook R: **The molecular mechanisms responsible for resistance in plant-pathogen interactions of the gene-for-gene type function more broadly than previously imagined.** *Proc Natl Acad Sci USA* 1998, **95**(17):9711-9712.
- Jones J, Dangl J: **The plant immune system.** *Nature* 2006, **444**(7117):323-329.
- Ingle R, Carstens M, Denby K: **Pamp recognition and the plant-pathogen arms race.** *BioEssays* 2006, **28**:880-889.
- Wang D, Weaver N, Kesarwani M, Dong X: **Induction of protein secretory pathway is required for systemic acquired resistance.** *Science* 2005, **308**(5724):1036-1040.
- Ribeiro D, Ribeiro O, Erwin D: **Phytophthora diseases worldwide.** *Amer Phytopathol Society, St. Paul, MN* 1996:561.
- Attard A, Gourgues M, Galiana E, Panabières F, Ponchet M, Keller H: **Strategies of attack and defense in plant-oomycete interactions, accentuated for *Phytophthora parasitica* dastur (syn. p. nicotianae brenda de haan).** *J Plant Physiol* 2008, **165**(1):83-94.
- Avrova A, Whisson S, Pritchard L, Venter E, De Luca S, Hein I, Birch P: **A novel non-protein-coding infection-specific gene family is clustered throughout the genome of *Phytophthora infestans*.** *Microbiology* 2007, **153**(Pt 3):747-759.
- Tyler BM, Tripathy S, Zhang X, Dehal P, Jiang RH, Aerts A, Arredondo FD, Baxter L, Bensasson D, Beynon JL, Chapman J, Damasceno CM, Dorrance AE, Dou D, Dickerman AW, Dubchak IL, Garbelotto M, Gijzen M, Gordon SG, Govers F, Grunwald NJ, Huang W, Ivors KL, Jones RW, Kamoun S, Kramps K, Lamour KH, Lee MK, McDonald WH, Medina M, Meijer HJ, Nordberg EK, Maclean DJ, Ospina-Giraldo MD, Morris PF, Phuntumart V, Putnam NH, Rash S, Rose JK, Sakihama Y, Salamov AA, Savidor A, Scheuring CF, Smith BM, Sobral BW, Terry A, Torto-Alalibo TA, Win J, Xu Z, Zhang H, Grigoriev IV, Rokhsar DS, Boore JL: **Phytophthora genome sequences uncover evolutionary origins and mechanisms of pathogenesis.** *Science* 2006, **313**(5791):1261-1266.
- de Wit P, Pieterse M, Govers F: **Molecular aspects of the potato - *Phytophthora infestans* interaction.** *European Journal of Plant Pathology* 1992, **98**(2):.
- Pieterse C, Derksen A, Folders J, Govers F: **Expression of the *Phytophthora infestans* ipib and ipio genes in planta and in vitro.** *Mol Gen Genet* 1994, **244**(3):269-277.
- Kamoun S, van West P, Jong A, Groot K, Vleeshouwers V, Govers F: **A gene encoding a protein elicitor of *Phytophthora infestans* is down-regulated during infection of potato.** *Mol Plant Microbe Interact* 1997, **10**(1):13-20.
- Bos J, Kanneganti T, Young C, Cakir C, Huitema E, Win J, Armstrong M, Birch P, Kamoun S: **The c-terminal half of *Phytophthora infestans* rxlr effector avr3a is sufficient to trigger r3a-mediated hypersensitivity and suppress infl-induced cell death in *Nicotianabenthiana*.** *Plant J* 2006, **48**(2):165-176.
- Kamoun S: **Groovy times: filamentous pathogen effectors revealed.** *Curr Opin Plant Biol* 2007, **10**(4):358-365.
- Halim V, Eschen-Lippold L, Altmann S, Birschwilks M, Scheel D, Rosahl S: **Salicylic acid is important for basal defense of *Solanum tuberosum* against *Phytophthora infestans*.** *Mol Plant Microbe Interact* 2007, **20**(11):1346-1352.
- Anand A, Uppalapati S, Ryu C, Allen S, Kang L, Tang Y, Mysore K: **Salicylic acid and systemic acquired resistance play a role in attenuating crown gall disease caused by *Agrobacterium tumefaciens*.** *Plant Physiol* 2008, **146**(2):703-715.
- Vleeshouwers V, Dooijeweert W, Govers F, Kamoun S, Colon LT: **The hypersensitive response is associated with host and non-host resistance to *Phytophthora infestans*.** *Planta* 2000, **210**:853-864.
- Richmond T, Somerville S: **Chasing the dream: plant est microarrays.** *Curr Opin Plant Biol* 2000, **3**(2):108-116.
- Moy P, Qutob D, Chapman B, Atkinson I, Gijzen M: **Patterns of gene expression upon infection of soybean plants by *Phytophthora sojae*.** *Mol Plant Microbe Interact* 2004, **17**(10):1051-1062.
- Silvar C, Merino F, Diaz J: **Differential activation of defense-related genes in susceptible and resistant pepper cultivars infected with *Phytophthora capsici*.** *J Plant Physiol* 2009, **165**(10):1120-1124.
- Tian Z, Liu J, Wang B, Xie C: **Screening and expression analysis of *Phytophthora infestans* induced genes in potato leaves with horizontal resistance.** *Plant Cell Rep* 2006, **25**(10):1094-1103.
- Wang G, Vega-Sanchez M, Gowda M: **Tag-based approaches for deep transcriptome analysis in plants.** *Plant Science* 2007, **173**:371-380.
- Cerami E, Bader G, Gross B, Sander C: **cpath: open source software for collecting, storing, and querying biological pathways.** *BMC Bioinformatics* 2006, **7**:497.
- Truesdell G, Dickman M: **Isolation of pathogen/stress-inducible cdnas from alfalfa by mrna differential display.** *Plant Mol Biol* 1993, **33**(4):737-743.
- Zhi Wu, Sheng Li, Yu Fen, Zi Sheng, Wu Xue, Xue Bao, Li F, Fu F, Sha L, Li W: **Identification of drought-responsive genes from maize inbred lines.** *Journal of plant physiology and molecular biology* 2006, **33**(6):607-611.
- Boller T, Collinge M, Beyer K, Binder A: **Identification of potato genes induced during colonization by *Phytophthora infestans*.** *Molecular Plant Pathology* 2001, **2**:125-134.
- Evers D, Ghislain M, Hausman J, Dommès J: **Differential gene expression in two potato lines differing in their resistance to *Phytophthora infestans*.** *J Plant Physiol* 2003, **160**(6):709-712.
- Restrepo S, Myers K, del Pozo O, Martin G, Hart A, Buell C, Fry W, Smart C: **Gene profiling of a compatible interaction between *Phytophthora infestans* and *Solanum tuberosum* suggests a role for carbonic anhydrase.** *Mol Plant Microbe Interact* 2005, **18**(9):913-922.

31. Duncan J, Lyon G, Birch P, Avrova A, Toth R: **Isolation of potato genes that are induced during an early stage of the hypersensitive response to *Phytophthora infestans*.** *MPMI* 1999, **12**:356-361.
32. Ronning CM, Stegalkina SS, Ascenzi RA, Bougri O, Hart AL, Utterbach TR, Vanaken SE, Riedmuller SB, White JA, Cho J, Pertea GM, Lee Y, Karamycheva S, Sultana R, Tsai J, Quackenbush J, Griffiths HM, Restrepo S, Smart CD, Fry WE, Hoeven R Van Der, Tanksley S, Zhang P, Jin H, Yamamoto ML, Baker BJ, Buell CR: **Comparative analyses of potato expressed sequence tag libraries.** *Plant Physiol* 2003, **131**(2):419-29.
33. Tian Z, Song B, Wang B, Liu J, Xie C: **Monitoring the expression patterns of potato genes associated with quantitative resistance to late blight during *Phytophthora infestans* infection using cDNA microarrays.** *Plant Science* 2005, **169**(6):1155-1167.
34. Glauser G, Grata E, Dubugnon L, Rudaz S, Farmer E, Wolfender J: **Spatial and temporal dynamics of jasmonate synthesis and accumulation in *Arabidopsis* in response to wounding.** *Biol Chem* 2008, **283**(24):16400-7.
35. Randall T, Lam S, Binder A, Boller T, Beyer K, Jimenez S, Collinge M: **Characterization of *Phytophthora infestans* genes regulated during the interaction with potato.** *Molecular Plant Pathology* 2002, **3**(6):473-485.
36. Le Berre J, Engler G, Panabières F: **Exploration of the late stages of the tomato-*Phytophthora parasitica* interactions through histological analysis and generation of expressed sequence tags.** *New Phytol* 2008, **177**(2):480-492.
37. Avrova A, Venter E, Birch P, Whisson S: **Profiling and quantifying differential gene transcription in *Phytophthora infestans* prior to and during the early stages of potato infection.** *Fungal Genet Biol* 2003, **40**(1):4-14.
38. Judelson H: **Genomics of the plant pathogenic oomycete *Phytophthora*: insights into biology and evolution.** *Adv Genet* 2007, **57**:97-141.
39. Lamour K, Win J, Kamoun S: **Oomycete genomics: new insights and future directions.** *FEMS Microbiol Lett* 2007, **274**(1):1-8.
40. Martin F, Bensasson D, Tyler B, Boore L: **Mitochondrial genome sequences and comparative genomics of *Phytophthora ramorum* and *P. sojae*.** *Curr Genet* 2007, **51**(5):285-296.
41. Huang S, Vossen E van der, Kuang H, Vleeshouwers V, Zhang N, Borm T, van Eck H, Baker B, Jacobsen E, Visser R: **Comparative genomics enabled the isolation of the *r3a* late blight resistance gene in potato.** *Plant J* 2005, **42**(2):251-261.
42. Whisson S, Torto T, Ochwo M, Birch P, Kamoun S, Jorunn B, Miles B, Armstrong M: **Intraspecific comparative genomics to identify avirulence genes from *Phytophthora*.** *New Phytol* 2003, **159**:63-72.
43. Kamoun S: **A catalogue of the effector secretome of plant pathogenic oomycetes.** *Annu Rev Phytopathol* 2006, **44**:41-60.
44. Gebhardt C, Valkonen J: **Organization of genes controlling disease resistance in the potato genome.** *Annu Rev Phytopathol* 2001, **39**:79-102.
45. Haldar K, Kamoun S, Hiller N, Bhattacharjee S, van Ooij C: **Common infection strategies of pathogenic eukaryotes.** *Nat Rev Microbiol* 2006, **4**(12):922-931.
46. Bhattacharjee S, Hiller N, Liolios K, Win J, Kanneganti T, Young C, Kamoun S, Haldar K: **The malarial host-targeting signal is conserved in the Irish potato famine pathogen.** *PLoS Pathogens* 2006, **2**(5):e50.
47. Rehmany A, Gordon A, Rose L, Allen R, Armstrong M, Whisson S, Kamoun S, Tyler B, Birch P, Beynon J: **Differential recognition of highly divergent downy mildew avirulence gene alleles by *rpp1* resistance genes from two *Arabidopsis* lines.** *Plant Cell* 2005, **17**(6):1839-1850.
48. Birch P, Rehmany A, Pritchard L, Kamoun S, Beynon J: **Trafficking arms: oomycete effectors enter host plant cells.** *Trends Microbiol* 2006, **14**(1):8-11.
49. Morgan W, Kamoun S: **Rxlr effectors of plant pathogenic oomycetes.** *Curr Opin Microbiol* 2007, **10**(4):332-338.
50. Hermann J, Westermann B, Neupert W: **Analysis of protein-protein interactions in mitochondria by coimmunoprecipitation and chemical cross-linking.** *Methods Cell Biol* 2001, **65**:217-230.
51. Bouarab K, Melton R, Peart J, Baulcombe D, Osbourn A: **A saponin-detoxifying enzyme mediates suppression of plant defenses.** *Nature* 2002, **418**(6900):889-892.
52. Darvill A, Rose J, Ham K, Albersheim P: **Molecular cloning and characterization of glucanase inhibitor proteins.** *Plant Cell* 2003, **14**:1329-1345.
53. Tian M, Huitema E, Cunha L, Torto-Alalibo T, Kamoun S: **A kazal-like extracellular serine protease inhibitor from *Phytophthora infestans* targets the tomato pathogenesis-related protease *p69b*.** *J Biol Chem* 2004, **279**(25):26370-26377.
54. Benedetti B, Tian M, Kamoun S: **A second kazal-like protease inhibitor from *Phytophthora infestans* inhibits and interacts with the apoplastic pathogenesis-related rotease *p69b* of tomato.** *Plant Physiology* 2005, **138**:1785-1793.
55. Tian M, Win J, Song J, Hoorntje R van der, Knaap E van der, Kamoun S: **A *Phytophthora infestans* cystatin-like protein targets a novel tomato papain-like apoplastic protease.** *Plant Physiol* 2007, **143**(1):P364-377.
56. Tyler B: **Molecular basis of recognition between *Phytophthora* pathogens and their hosts.** *Annu Rev Phytopathol* 2002, **40**:137-167.
57. Lee T Van der, Robold A, Testa A, Klooster J, Govers F: **Mapping of avirulence genes in *Phytophthora infestans* with amplified fragment length polymorphism markers selected by bulked segregant analysis.** *Genetics* 2001, **157**(3):949-956.
58. Armstrong M, Whisson S, Pritchard L, Bos J, Venter E, Avrova A, Rehmany A, Ulrike Bohme, Brooks K, Cherevach I, Hamlin N, White B, Fraser A, Lord A, Quail M, Churcher C, Hall N, Berriman M, Huang S, Kamoun S, Beynon J, Birch P: **An ancestral oomycete locus contains late blight avirulence gene *avr3a*, encoding a protein that is recognized in the host cytoplasm.** *Proc Natl Acad Sci USA* 2005, **102**(21):7766-7771.
59. Bent A, Mackey D: **Elicitors, effectors, and *r* genes: the new paradigm and a lifetime supply of questions.** *Annu Rev Phytopathol* 2007, **45**:399-436.
60. Dyer M, Murali M, Sobral B: **Computational prediction of host-pathogen protein-protein interactions.** *Bioinformatics* 2007, **23**(13):i159-i166.
61. Aggarwal K, Lee K: **Functional genomics and proteomics as a foundation for systems biology.** *Briefings in functional genomics and proteomics* 2003, **2**:175-184.
62. Katagiri F: **A global view of defense gene expression regulation: a highly interconnected signaling network.** *Curr Opin Plant Biol* 2004, **7**(5):506-511.
63. Cubero J, Lastra B, Salcedo C, Piquier J, López M: **Systemic movement of *Agrobacterium tumefaciens* in several plant species.** *J Appl Microbiol* 2006, **101**(2):412-421.
64. Masoudi-Nejad A, Goto S, Endo T, Kanehisa M: **Kegg bioinformatics resource for plant genomics research.** *Methods Mol Biol* 2007, **406**:437-458.
65. Evans T, Gillespie C, Wilkinson D: **The sbml discrete stochastic models test suite.** *Bioinformatics* 2008, **24**(2):285-286.
66. Finney A, Hucka M: **Systems biology markup language: Level 2 and beyond.** *Biochem Soc Trans* 2003, **31**(Pt 6):1472-1473.
67. Albrecht M, Huthmacher C, Tosatto S, Lengauer T: **Decomposing protein networks into domain-domain interactions.** *Bioinformatics* 2005, **21**(Suppl 2):ii220-ii221.
68. Bell G, Lewitter F: **Visualizing networks.** *Methods Enzymol* 2006, **411**:408-421.
69. Horsfall J, Waggoner P: **Epidem a simulator of plant disease written for a computer.** *Conn agric Exp Stn Bull* 1969, **698**:80.
70. Zadocks J, Rainey R, Mollison D, Tyrrell D, Fitt B: **Twenty-five years of botanical epidemiology (and discussion).** *Philosophical Transactions of the Royal Society of London* 1988, **321**:377-387.
71. Billard L, Dayananda P, Chakraborty S: **Estimation of rate parameter and its relationship with latent and infectious periods in plant disease epidemics.** *Biometrics* 1995, **51**:284-292.
72. Billard L: **Some statistical opportunities in the agricultural sciences.** *The Canadian Journal of Statistics* 1998, **3**(26):392-404.
73. Metah Y, Zadocks J: **uredospore production and sporulation period of *Puccinia recondita* f.sp. *trititica* on primary leaves of wheat.** *Netherlands journal of plant pathology* 1970, **76**:267-276.
74. Vleeshouwers V, Van Dooijeweert W, Govers F, Kamoun S, Colon L: **Does basal pr gene expression in *Solanum* species contribute to non-specific resistance to *Phytophthora infestans*?** *Physiological and Molecular Plant Pathology* 2000, **57**:35-42.
75. Ristaino J, Gumpertz M: **New frontiers in the study of dispersal and spatial analysis of epidemics caused by species in the genus *Phytophthora*.** *Annu Rev Phytopathol* 2000, **38**:541-576.

76. Madden H, Hughes G, Bosch F: **The study of plant disease epidemics.** In *The American Phytopathological Society APS Press* St. Paul, Minnesota; 2007.
77. Fry W, Minoque K: **Models for the spread of plant disease: model description.** *Phytopathology* 1983, **73**:168-73.
78. Fry W, Minoque K: **Models for the spread of plant disease: some experimental results.** *Phytopathology* 1983, **73**:1173-76.
79. Ferrandino F: **Dispersive epidemic waves: I. focus expansion in a linear planting.** *Phytopathology* 1993, **798(83)**:802.
80. Bosch F van den, Zadoks J: **On the spread of plant disease: a theory on foci.** *Annu Rev Phytopathol* 1994, **32**:503-21.
81. Sherm H: **On the velocity of epidemic waves in model plant disease epidemics.** *Ecol Model* 1996, **87**:217-22.
82. Bolker B: **Analytic models for the patchy spread of plant disease.** *Bull Math Biol* 1999, **61**:849-874.
83. Gani J, Jerwood D: **The cost of a general stochastic epidemic.** *Journal of Applied Probability* 1972, **9(2)**:257-269.
84. Marcus R: **Deterministic and stochastic logistic models for describing increase of plant disease.** *Crop Protection* 1991, **10**:155-159.
85. Grand L, Benson D, Gottwald T, Vernia C: **Temporal and spatial epidemiology of phytophthora root rot in Fraser fir plantations.** *Phytopathology* 2006, **90(9)**:1171-1180.
86. Mayton H, Aylor D, Fry W, Andrade-Piedra J: **Quantifying the rate of release and escape of Phytophthora infestans sporangia from a potato canopy.** *Phytopathology* 2001, **91(12)**:1189-1196.
87. Xu M, Ridout X: **Stochastic simulation of the spread of race-specific and race-nonspecific aerial fungal pathogens in cultivar mixtures.** *Plant Pathology* 2000, **49(2)**:207-218.
88. Alm E, Arkin A: **Biological networks.** *Curr Opin Struct Biol* 2003, **13(2)**:193-202.
89. Aguda BD, Goryachev AB: **From pathways databases to network models of switching behavior.** *PLoS Comput Biol* 2007, **3(9)**:1674-1678.
90. Vidal M: **Interactome modeling.** *FEBS Lett* 2005, **579(8)**:1834-1838.
91. Davis F, Barkan D, Eswar N, McKerrow J, Sali A: **Host pathogen protein interactions predicted by comparative modeling.** *Protein Sci* 2007, **16(12)**:2585-2596.
92. Li P, Zhang C, Perkins E, Gong P, Deng Y: **Comparison of probabilistic boolean network and dynamic bayesian network approaches for inferring gene regulatory networks.** *BMC Bioinformatics* 2007, **8(Suppl 7)**:S13.
93. Colizza V, Maritanb A, Flamminia A, Vespignani A: **Characterization and modeling of protein-protein interaction networks.** *Physica A: Statistical Mechanics and its Applications. Physics Applied to Biological Systems, Physics Applied to Biological Systems* 2005, **35**:1-27.
94. Freitas R, Santos , Chen Z, Batista M, Duarte J, Borges A, Texeira A, Ferreira R, Monteiro S: **The role of plant defense proteins in fungal pathogenesis.** *Molecular Plant Pathology* 2007, **8(5)**:677-700.
95. Govers F, Gijzen M: **Phytophthora genomics: the plant destroyers' genome decoded.** *Mol Plant Microbe Interact* 2006, **19(12)**:1295-1301.
96. Gupta M, Qu P, Ibrahim J: **A temporal hidden markov regression model for the analysis of gene regulatory networks.** *Biostatistics* 2007, **8(4)**:805-820.
97. Won K, Sandelin a, Marstrand T, Krogh A: **Modeling promoter grammars with evolving hidden markov models.** *Bioinformatics* 2008, **24(15)**:1669-1675.
98. Genoud T, Trevino M, Métraux J: **Numeric simulation of plant signaling networks.** *Plant Physiol* 2001, **126(4)**:1430-1437.
99. Honda H, Hakamada K, Hanai T, Kobayashi T: **A preprocessing method for inferring genetic interaction from gene expression data using boolean algorithm.** *Journal of Bioscience and Bioengineering* 2004, **98**:457-463.
100. Gupta R, Achenie L: **A network model for gene regulation.** *Computers and Chemical Engineering* 2006, **31(8)**:950-961.
101. Campbell C: **Interpretation and uses of diseases progress curves for root diseases.** In *Plant Disease Epidemiology: Population Dynamics of Management Volume 1*. Edited by: Jones AL, Leonard KJ, Fry WE. New York: MacMillan; 1986:38-54.
102. Kishalappa A, Ludwig A: **Calculation of apparent infection rate in plant diseases: Development of a method to correct for host growth.** *Phytopathology* 1982, **72**:1373-1377.
103. Kester D, Fenton C, Kuniyuski C: **Models for noninfectious bud failure in almonds.** *Phytopathology* 1988, **78**:139-143.
104. Vander Plank J: **Plant diseases: Epidemic and control.** Academic Press. New York; 1963.
105. Vander Plank JE: **Host-pathogen interactions in plant disease.** Academic Press. New York; 1982.
106. Sugiyama Y, Watase Y, Nagase M, Makita N, Yagura S, Hirai A, Sugiura M: **The complete nucleotide sequence and multipartite organization of the tobacco mitochondrial genome: comparative analysis of mitochondrial genomes in higher plants.** *Mol Genet Genomics* 2005, **272(6)**:603-615.
107. Yukawa M, Tsudzuki T, Sugiura M: **The chloroplast genome of *Micotiana sylvestris* and *Nicotiana tomentosiformis*: complete sequencing confirms that the *Nicotiana sylvestris* progenitor is the maternal genome donor of *Nicotiana tabacum*.** *Mol Genet Genomics* 2006, **275**:367-373.
108. Vezzi A, Scotti N, Gray JC, Valle G, Grillo S, Gargano D, Cardi T: **The complete nucleotide sequence of potato (*Solanum tuberosum* cv. Desiree) chloroplast dna.** *Abstracts 2nd Solanaceae genome workshop* 2005.
109. Greivich J, Sasaki C, Quesada-Vargas T, Guda C, Tomkins J, Jansen RK, Daniell H, Lee SB: **Complete chloroplast genome sequences of *Solanum bulbocastanum*, *Solanum lycopersicum* and comparative analyses with other solanaceae genomes.** *Theor Appl Genet* 2006, **8**:112.
110. Kahlau S, Aspinall S, Gray J, Bock R: **Sequence of the tomato chloroplast dna and evolutionary comparison of solanaceous plastid genomes.** *J Mol Evol* 2006, **63(2)**:194-207.
111. Yukawa M, Tsudzuki T, Sugiura M: **The chloroplast genome of *Nicotiana sylvestris* and *Nicotiana tomentosiformis*: complete sequencing confirms that the *Nicotiana sylvestris* progenitor is the maternal genome donor of *Nicotiana tabacum*.** *Mol Genet Genomics* 2006, **275(4)**:367-373.
112. Schmitz C, Regel R, Du T, Hupfer H, Herrmann R, Maier R: **The plastid chromosome of *Atropa belladonna* and its comparison with that of *Nicotiana tabacum*: the role of rna editing in generating divergence in the process of plant speciation.** *Mol Biol Evol* 2002, **19(9)**:1602-1612.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

