

## EDITORIAL

# Personalizing medicine: a systems biology perspective

*Molecular Systems Biology* 17 March 2009; doi:10.1038/msb.2009.8

This is an open-access article distributed under the terms of the Creative Commons Attribution Licence, which permits distribution and reproduction in any medium, provided the original author and source are credited. This licence does not permit commercial exploitation or the creation of derivative works without specific permission.

## 'How to shift from population-based data toward personal health care?'

According to the SEER Cancer Statistics Review, between 1975 and 2005, the deaths from heart disease in the United States declined from 37.8 to 26.6%, whereas over the same period those from cancer increased from 19.2 to 22.8% (Ries *et al*, 2008). In the US alone, it is estimated that in 2008 a total of 565,650 patients will have died from cancer, whereas 1,437,180 will have been newly diagnosed (Jemal *et al*, 2008). Thus, despite undeniable advancements in early diagnostics and progress in reducing morbidity through therapeutic efforts, it appears that after spending billions of dollars on oncology research since 1971, more than three decades later the 'war on cancer' is still far from being won ([http://dtp.nci.nih.gov/timeline/noflash/milestones/M4\\_Nixon.htm](http://dtp.nci.nih.gov/timeline/noflash/milestones/M4_Nixon.htm)).

Although pressure from patients, advocacy groups and funding agencies is mounting, the conventional population-based approach for therapeutic developments in clinics still relies on passing a series of randomized controlled trials that depend on enrollment of many patients in search for favorable yet averaged outcome patterns that statistically document safety and efficacy. Research and development (R&D) of a new therapeutic drug now takes 10–15 years at a cost in excess of US\$1.3 billion, with only 20% of marketed drugs producing revenues that match or exceed their R&D costs (Pharmaceutical Research and Manufacturers of America, 2008). Fueled by the comparably modest progress made so far in pursuing this expensive conventional route, there has been much interest lately in moving toward personalized or patient-specific medicine. For oncology, for instance, 'specific' refers to assessing not only tumor type, size, location, patient age and many other parameters that are already used and that result in the conventional grading and staging of the disease; rather, it argues for incorporating also the molecular fingerprint, or signature, and associated growth kinetics of the patient's tumor when fine-tuning treatment regimen on a case-by-case basis (Roukos *et al*, 2007). As everyone's tumor is distinct, to a degree, the 'one-size-fits-all' treatment strategy cannot work, so the new paradigm.

Although few would argue against the rationale behind the concept *per se*, what remains unclear, however, is how to actually process personalized medicine when the costs on the diagnostic side, such as that for advanced personalized

molecular screenings, cease to be the limiting factor due to a wide range of ongoing biomedical engineering efforts (e.g. Shendure *et al*, 2008). Next steps will involve having to address as to how to design, run and evaluate clinical trials in this new era, and how to administer personalized health care in reality. That is, (1) following the new paradigm, the averaged results derived from randomized clinical trials will offer insufficient if not even incorrect guidance on how to approach a specific case. Patient responses to a particular drug, for instance, are known to fall into a more or less wide range that deviates from the averaged behavior, a fact that is being made chiefly responsible for why a particular drug works better in some than in others. Although, in an effort to limit adverse side effects for the patient population at large, toxicity testing will likely have to continue to rely on a conventional trial-based approach, efficacy assessment will have to reflect the new paradigm in one form or another. (2) An equally significant challenge looms on the day-to-day operations side in clinics where at any point in time, multiple, slightly varied treatment protocols will have to be designed, administered, monitored and adjusted if need be. At the very least, that puts considerable strains on the existing infrastructure. Also, enrollment numbers will be small, in theory down to one patient per modified regimen, with the obvious consequence that clinical institutions will have to pool and exchange such case-centric data and expertise so that new patients can benefit from past experience. (3) Even if a compound survives the elaborate evaluation processes in the current pharmaceutical 'pipeline,' by the time it becomes available, it lags several years behind the pace of basic research that continued while the drug was under development. Consequently, new data would have become available that may point toward different, or higher valued targets, or even question the rationale of the initially chosen strategy altogether. Short of starting the development process all over and facing the same dilemma again in a few years, a workflow has to be designed that allows including new R&D insights, also from this new case-centric medicine, into the development process in an effort to improve the drug's efficacy at later stages in the pipeline—without compromising patient safety and at acceptable costs for industry.

This leads to a key question. As, at least in the early stages, this necessary move toward personalized medicine ideally has to build on available population data, how can we consolidate

both seemingly distinctively different approaches? Also, this shift will likely come with a hefty price tag as it requires design and development of massive data storage, mining and transfer capabilities, efficiently linked through innovative web-based workflows. It is here where systems biology (e.g. Coffey, 1998; Ahn *et al*, 2006; Hornberg *et al*, 2006; Liu *et al*, 2006) or, more precisely, *computational systems medicine* can make all the difference. At the core of all this is the quest to gain insights into the intricacies of nonlinear structure–function relationships, across multiple resolutions, in space and time. Through its quantitative strengths, systems biology already generates invaluable fundamental insights into the organization, functions and dysfunctions of biological networks (Kitano, 2002; Chuang *et al*, 2007; Yildirim *et al*, 2007; Zhu *et al*, 2008). It has also recently begun to tackle the critical issues of the integration of biomedical data across scales and from diverse sources (Deisboeck *et al*, 2009). However, the field is still in its infancy and has yet to deliver *applied solutions* for the life sciences in general and medicine in particular.

## Two scenarios

To exemplify how these approaches can eventually be integrated into more conventional workflows, and why this should constitute ‘added value’, I briefly introduce two scenarios inspired from our own works on computational cancer biology.

(A) Incorporating a comprehensive data set from a patient (e.g. molecular biomarker, histology, and imaging data) into an advanced computational modeling platform (e.g. Wang and Deisboeck, 2008; Zhang *et al*, 2009) and then training the model on this patient’s data as they come forward, will necessarily yield a more accurate description of the *specific* kinetics of disease progression or treatment outcome; hence, this approach should provide a higher predictive power than that achieved with pooled data only and thus help guide treatment strategies more accurately en route to improving outcome. However, in practice, it is likely that not all data are available at all time points for such a patient-specific model. In this case, one could approximate the missing data sets from published randomized trials both from controls and from groups that have been treated with a similar protocol. These population-based data would yield target ranges for the computer model to explore numerically which missing data profile fits best to match the patient’s observed tumor growth patterns. The result is an ‘*ad hoc*’ combination of population-based and patient-specific methods where, conceivably, one could determine how much personal information is necessary, at what time point, to run a sufficiently meaningful personalized model. This supports the notion of an *in silico* informed, customized management of follow-up diagnostics where expensive exams are spread sufficiently thin without compromising the necessary monitoring of the disease under treatment. The value proposition, in addition to outcome improvement (with shortened hospital stay and reduced productivity loss), is that the cost savings from not having to collect all data from a specific patient at all time points, for many cases, outweigh the steep expenditures of the remaining population-based approaches, which also would likely enroll

less patients to begin with should the new paradigm gain ground (in turn, limiting costs even more).

(B) For the time being, target discovery in the pharmaceutical industry is still driven by data from *in vitro* and *in vivo* studies, as well as proprietary or published, yet mostly pooled clinical data. To be fair, customizing any compound from the get-go to a particular patient is, at least for the time being, prohibitively costly and thus a non-viable R&D strategy. It is here where another related systems biology effort will have impact: identifying *biomarkers* that strongly correlate with the cancer system’s dynamics (Sawyers, 2008), hence robustly reflect grading and thus allow proper staging of the disease. Using computational modeling (Wang *et al*, 2008), one could first characterize a patient’s specific biomarkers (ranging from critical pathway proteins to phenotypic profiles and imaging patterns) and then compare these ‘cross-scale signatures’ with those seen in pooled data from conventional clinical practice or from a trial with the candidate drug being applied. Similarities much like distinct differences could potentially be correlated with the average outcome observed and thus exploited by proactively adjusting the treatment regimen in the particular case at hand in the interest of optimizing therapeutic outcome. In the process, these personalized, biomarker–outcome relationship data can be properly IT warehoused and the resulting databases can be mined for designing future, more focused trials and to improve such biomarker-based, patient-specific ‘consulting’ in going forward.

These examples are by no means intended to be exhaustive and any combination of these and related scenarios is conceivable. They are merely meant to demonstrate that a merger between the two paradigms, brokered by computational systems medicine, can facilitate the breakthrough of personalization and add value to population-based approaches, without having to abandon conventional methods and techniques in clinics and pharmaceutical industry altogether. Of course, there are many challenges involved in making all this happen. Technical obstacles reach from yet limited scalability of *in silico* models and necessary standardizations of input data across platforms (Kuo *et al*, 2006), to advanced workflow design and implementation (Deisboeck *et al*, 2007), and data safety and confidentiality measures (Lunshof *et al*, 2008). Although any one of these challenges is formidable, they present intriguing opportunities for innovation, certainly worth pursuing given the promise personalizing medicine holds for patients and health-care industry alike.

## Conclusions

Owing to an aging baby boomer generation, the US Census Bureau projects the age group of 65 years and older to increase from 38.7 million US residents in 2008 to 88.5 million by 2050 (<http://www.census2010.gov/Press-Release/www/releases/archives/population/012496.html>). Demands on an already stretched health-care system will be staggering and calls for a more innovative, and ultimately more effective management of R&D in industry and academic medicine will almost certainly become louder. The *status quo* strategy in medical practice is as simple as it now appears to be intrinsically flawed: carefully assess a patient’s symptoms to diagnose his

specific disease patterns only to then treat it with a protocol that is based on the assumption that most interpersonal characteristics are rather inconsequential for treatment outcome. However, most diseases such as cancer are distinctively heterogeneous, in itself and across the population and as such, these characteristics should matter for prediction and real outcome *per se*. That is not to say that population-based medicine will cease to play an important albeit changing, more supportive role; confirming that a majority of patients respond favorably to a particular treatment, with what is believed to be acceptable side effects, remains critical information in assessing the averaged risk–benefit of any new treatment for the population at large. However, even if by these standards a new drug has been deemed advantageous, we must understand why it works in most and why it fails in *some*, a process that will inevitably lead toward higher data specificity. Diagnosing a disease in a particular patient to an ever greater level of granularity and then tuning treatment to precisely this information, case-by-case, is the central idea behind personalizing medicine. As detailed above, and despite all technical challenges involved, there is good reason for integrating population and personalized medicine in going forward, not the least of it to control an otherwise prohibitive increase in costs. In coming off age, computational systems medicine holds great promise to support and eventually even guide this effort, and thus to help facilitate this important paradigm shift in the health-care industry.

## Acknowledgements

This study has been supported in part by NIH grant CA 113004 and by the Harvard-MIT (HST) Athinoula A Martinos Center for Biomedical Imaging and the Department of Radiology at Massachusetts General Hospital. I thank Dr Jose Costa (Yale University Medical School) and Dr Robert Gatenby (Lee Moffitt Cancer Center) for a critical review of the paper, and Dr Zhihui Wang (Massachusetts General Hospital) for help in formatting the text.

**Thomas S Deisboeck**

Complex Biosystems Modeling Laboratory, Harvard-MIT (HST) Athinoula A Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital-East, 2301, Building 149, 13th Street, Charlestown, MA 02129, USA

## References

- Ahn AC, Tewari M, Poon CS, Phillips RS (2006) The clinical applications of a systems approach. *PLoS Med* **3**: e209
- Chuang HY, Lee E, Liu YT, Lee D, Ideker T (2007) Network-based classification of breast cancer metastasis. *Mol Sys Biol* **3**:140
- Coffey DS (1998) Self-organization, complexity and chaos: the new biology for medicine. *Nat Med* **4**: 882–885
- Deisboeck TS, Zhang L, Martin S (2007) Advancing cancer systems biology: introducing the Center for the Development of a Virtual Tumor, CViT. *Cancer Inform (Syst Biol Special Issue)* **2**: 1–8
- Deisboeck TS, Zhang L, Yoon J, Costa J (2009) *In silico* cancer modeling: ready for primetime? *Nat Clin Pract Oncol* **6**: 34–42
- Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J (2006) Cancer: a systems biology disease. *Biosystems* **83**: 81–90
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ (2008) Cancer statistics, 2008. *CA Cancer J Clin* **58**: 71–96
- Kitano H (2002) Computational systems biology. *Nature* **420**: 206–210
- Kuo WP, Liu F, Trimarchi J, Punzo C, Lombardi M, Sarang J, Whipple ME, Maysuria M, Serikawa K, Lee SY, McCrann D, Kang J, Shearstone JR, Burke J, Park DJ, Wang X, Rector TL, Ricciardi-Castagnoli P, Perrin S, Choi S *et al.* (2006) A sequence-oriented comparison of gene expression measurements across different hybridization-based technologies. *Nat Biotechnol* **24**: 832–840
- Liu ET, Kuznetsov VA, Miller LD (2006) In the pursuit of complexity: systems medicine in cancer biology. *Cancer Cell* **9**: 245–247
- Lunshof JE, Chadwick R, Vorhaus DB, Church GM (2008) From genetic privacy to open consent. *Nat Rev Genet* **9**: 406–411
- Pharmaceutical Research and Manufacturers of America (2008) *Pharmaceutical Industry Profile 2008*. Washington, DC: PhRMA, March 2008; <http://www.phrma.org/files/2008%20Profile.pdf>
- Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlander N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (2008) *SEER Cancer Statistics Review, 1975–2005*. Bethesda, MD: National Cancer Institute [http://seer.cancer.gov/csr/1975\\_2005/](http://seer.cancer.gov/csr/1975_2005/) based on November 2007 SEER data submission, posted to the SEER website
- Roukos DH, Murray S, Briasoulis E (2007) Molecular genetic tools shape a roadmap towards a more accurate prognostic prediction and personalized management of cancer. *Cancer Biol Ther* **6**: 308–312
- Sawyers CL (2008) The cancer biomarker problem. *Nature* **452**: 548–552
- Shendure JA, Porreca GJ, Church GM (2008) Overview of DNA sequencing strategies. *Curr Protoc Mol Biol*. Chapter 7: Unit 7.1
- Wang Z, Birch CM, Deisboeck TS (2008) Cross-scale sensitivity analysis of a non-small cell lung cancer model: linking molecular signaling properties to cellular behavior. *Biosystems* **92**: 249–258
- Wang Z, Deisboeck TS (2008) Computational modeling of brain tumors: discrete, continuum or hybrid? *Sci Model Simul* **15**: 381–393
- Yildirim MA, Goh KI, Cusick ME, Barabási AL, Vidal M (2007) Drug-target network. *Nat Biotechnol* **25**: 1119–1126
- Zhang L, Wang Z, Sagotsky JA, Deisboeck TS (2009) Multiscale agent-based cancer modeling. *J Math Biol* **58**: 545–559
- Zhu J, Zhang B, Schadt EE (2008) A systems biology approach to drug discovery. *Adv Genet* **60**: 603–635



*Molecular Systems Biology* is an open-access journal published by *European Molecular Biology Organization* and *Nature Publishing Group*.

This article is licensed under a Creative Commons Attribution-NonCommercial-No Derivative Works 3.0 Licence.