Method S1: Mathematical Analysis of input–coupled positive feedback and emergent behaviors related to Figure 5

General framework

Assumptions and conclusions

We consider two models of increasing complexity for the dynamics in the system describing PINK1–Parkin–Ubiquitin on a Mitochondrion discussed in the main body of the paper. Simplifying somewhat, we may say that in the experiment the amount $P(t)$ at time t of Parkin on a mitochondrion is tracked as it grows until it reaches a certain detection level P_{det}. The initial amount of Parkin P_{init} is assumed to be much smaller than the detection level P_{det}. This yields a measurement of the time T it takes the Parkin level to grow from P_{init} to P_{det}. The level E of PINK1 affects the rate at which Parkin increases and thus the experiment gives us a measurement of the growth time T as a function of the PINK1 level E.

The main assumptions concerning the system that we make are

i. The system contains a positive feedback mechanism
ii. PINK1 acts as a catalyst: some of the reaction rates in the system increase when the amount of PINK1 is increased
iii. P_{init} is much smaller than P_{det}
iv. The rate at which free Ubiquitin spontaneously moves to the mitochondrion is relatively small and may be ignored
v. The amounts of free Ubiquitin and Parkin are large compared to P_{det} and may be considered constant

These assumptions lead to the following consequences:

Exponential Growth: The amount of Parkin grows (or decays) exponentially; if $P(t)$ is the amount of Parkin at time t, then the models predict $P(t) \approx P_{\text{init}} e^{\lambda_E t}$, where the growth rate λ_E depends on the many reaction rates in the model, and in particular on the amount E of PINK1 in the system.

Threshold for circuit activation: There is a critical value E_* such that $\lambda_E < 0$ when $E < E_*$ and such that $\lambda_E > 0$ when $E > E_*$. This means that if the PINK1 amount is below E_* the Parkin levels will decrease exponentially, and if the PINK1 amount exceeds E_* then Parkin will grow exponentially.

Time to detection decreases with increasing PINK1 levels: The exponent λ_E is an increasing function of the PINK1 level E. When $\lambda_E > 0$ the Parkin level grows exponentially according to

$$P(t) \approx P(0) e^{\lambda_E t}.$$

Let P_{det} be the minimal level at which Parkin is detected, and assume that the initial amount P_{init} of Parkin is small compared to P_{det}. If the growth rate λ_E is negative then the amount

$P(t)$ of Parkin will only decay and thus never reach the detection level. On the other hand, if the growth rate λ_E is positive, then the detection time $T_{\text{det}}(E)$ follows from

$$(1) \qquad P(T_{\text{det}}) = P_{\text{det}} \iff P_{\text{init}} e^{\lambda_E T_{\text{det}}} = P_{\text{det}} \iff T_{\text{det}} = \frac{\ln(P_{\text{det}}/P_{\text{init}})}{\lambda_E}.$$

For each of the models we find that the growth rate λ_E increases when E is increased, which therefore implies that the time to detection T_{det} is a decreasing function of E.

The inverse law

In the minimal model one finds that there is a minimal PINK1 level E_* such that the system does not activate if $E \leq E_*$, in which case the time to detection should be considered infinite. For $E > E_*$ the time to detection in the minimal model is given by an inverse law of the form

$$(2) \qquad T_{\text{det}} = \frac{C_*}{E - E_*}$$

for some constant C_*, i.e. the time to detection is inversely proportional to $E - E_*$, which is the amount of PINK1 above the critical value E_*. See (Eq. 11) for a derivation of this law in the minimal model case.

In the general model the inverse law still holds approximately. We can justify this theoretically for values of E close to the critical level E_*, and also for very large values of E. Numerical computations (see Appendix Figure 1) indicate that the approximation also holds for intermediate PINK1 levels.

For PINK1 values E that are close to the critical value E_* it follows from Lemma 4 that

$$\frac{\partial \lambda}{\partial E}(E_*) > 0.$$

If $E \approx E_*$ then

$$\lambda(E) \approx \frac{\partial \lambda}{\partial E}(E_*)\big(E - E_*\big),$$

and thus, if $E > E_*$ and if $E - E_*$ is small, then

$$(3) \qquad T_{\text{det}}(E) = \frac{\ln P_{\text{det}}/P_{\text{init}}}{\lambda_E} \approx \frac{C_*}{E - E_*}, \quad \text{with } C_* = \frac{\ln\big(P_{\text{det}}/P_{\text{init}}\big)}{\frac{\partial \lambda}{\partial E}(E_*)}.$$

We will also show that as $E \to \infty$, the dominant eigenvalue converges to a limiting value λ_∞ (see (Eq. 15)), and that $\lambda(E)$ is a strictly increasing function of E for all $E > E_*$. It follows that $T_{\text{det}}(E)$ has a limiting value T_∞ for very large E. Moreover, (Eq. 15) also implies that, for a suitably chosen constant C_∞ depending on the parameters k_i, one has

$$(4) \qquad T_{\text{det}}(E) \approx \frac{C_\infty}{E - E_*} + T_\infty.$$

Thus the graph of T_{det} vs. E has both horizontal and vertical asymptotes, and approaches both asymptotes like a hyperbola.

General form of the models

In each of the models we have a vector

$$S(t) = \begin{bmatrix} s_1(t) \\ \vdots \\ s_n(t) \end{bmatrix}$$

containing the total amounts of the components that the model tracks, such as Parkin, Ubiquitin, (phosphorylated or not), or combinations of these. Using mass action kinetics we arrive at a system of differential equations governing the time dependence of $S(t)$. Assuming that we only consider the system when the amounts of non-free Parkin and Ubiquitin are small, we arrive at a linear system

$$S'(t) = \mathcal{M}S(t), \tag{5}$$

where

- E is the amount of PINK1 in the system; this quantity is assumed to be kept constant;
- $\mathcal{M}$ is a matrix containing the reaction rates, and which can be further decomposed as

  $$\mathcal{M} = \mathcal{M}_0 + E\mathcal{M}_1.$$

  The matrix $\mathcal{M}_0$ contains the rates at which reactions take place in the absence of PINK1, while $\mathcal{M}_1$ accounts for the change in the reaction rates caused by the presence of PINK1.

Eigenvalue analysis of the models

Using the method of eigenvalues and vectors one shows that the general solution of a linear equation such as (Eq. 5) is a superposition of exponentially growing or decaying terms, i.e.

$$S(t) = e^{\lambda_1 t}V_1 + e^{\lambda_2 t}V_2 + \cdots + e^{\lambda_n t}V_n \tag{6}$$

in which $\lambda_1, \ldots, \lambda_n$ are the eigenvalues of the matrix $\mathcal{M}$, $V_1, \ldots, V_n$ are corresponding eigenvectors. Since we are interested in the time it takes $S(t)$ to grow from a small initial amount to the detection value, we want to consider the fastest growing term(s) in (Eq. 6), i.e. the terms corresponding to the largest eigenvalues λ_i. In studying the eigenvalues $\lambda_1, \ldots, \lambda_n$ we note that in all versions of our model the matrix $\mathcal{M}$ has non-negative off-diagonal entries, and is irreducible. This implies, by the Perron-Frobenius theorem, that $\mathcal{M}$ has a unique dominant eigenvalue. If we renumber the eigenvalues so that λ_{dom}, is the dominant eigenvalue, then

i. λ_{dom} is a real eigenvalue of $\mathcal{M}$ (not a complex eigenvalue)
ii. every other (possibly complex) eigenvalue μ of $\mathcal{M}$ satisfies $\operatorname{Re}\mu < \lambda_{\text{dom}}$
iii. corresponding to the eigenvalue λ_{dom}, the matrix $\mathcal{M}$ has positive left and right eigenvectors $W_{\text{dom}}, V_{\text{dom}}$ respectively; by definition these satisfy

  $$\mathcal{M}V_{\text{dom}} = \lambda_{\text{dom}}V_{\text{dom}}, \qquad \mathcal{M}^\top W_{\text{dom}} = \lambda_{\text{dom}}W_{\text{dom}}.$$

  They can be normalized so that $\langle W_{\text{dom}}, V_{\text{dom}}\rangle = 1$.

The dominant eigenvalue tells us the largest exponential rate with which solutions to (Eq. 5) can grow. More precisely, the eigenvalue decomposition (Eq. 6) contains one term corresponding to the dominant eigenvalue λ_{dom}. If we denote this term by $s(t)V_{\text{dom}}$ and group the remaining terms into a slower growing component $S^{\circ}(t)$ then we have

$$S(t) = s(t)V_{\text{dom}} + S^{\circ}(t), \qquad \langle W_{\text{dom}}, S^{\circ}(t)\rangle = 0. \tag{7}$$

The left-eigenvector W_{dom} allows one to find the coefficient $s(t)$ from the vector $S(t)$ via

$$s(t) = \langle W_{\text{dom}}, S(t)\rangle.$$

By taking the inner product with W_{dom} on both sides in (Eq. 5) one finds that the V_{dom} component of S satisfies an ordinary differential equation

$$s'(t) = \lambda_{\text{dom}} s(t), \tag{8}$$

whose solution can be written as

$$s(t) = e^{\lambda_{\text{dom}} t} s(0) \tag{9}$$

To compute the time to detection we assume that Parkin is detected when $s(t)$ reaches a specific detection value x_{det}. Then the time to detection is

$$T_{\text{det}} = \frac{1}{\lambda_{\text{dom}}} \ln \frac{s_{\text{det}}}{s(0)}.$$

The minimal PINK1-Parkin model

In our simplest model we only keep track of the Parkin in the system, assuming it exists in one of two states: on the mitochondria or free (not on the mitochondria).

Parkin on the mitochondria can bind free Parkin and this process is aided by PINK1 as an enzymatic catalyst. Parkin on the mitochondria also spontaneously leaves the mitochondria.

Our model keeps track of the following quantities:

X_{tot}	total amount of Parkin in the system; a constant
X_{p}	amount of Parkin on the mitochondria (referred to as "pX" in the main text)
X	amount of free Parkin, $X + X_{\text{p}} = X_{\text{tot}}$
E	amount of PINK1 in the system; constant in time

Since X_{tot} and E are time independent and since X_{p} and X are constrained by $X_{\text{p}} + X = X_{\text{tot}}$, the time evolution of the system is completely determined by that of X_{p} . The following differential equation takes both recruitment and degradation into account:

$$\frac{dX_{\text{p}}}{dt} = k_{\text{fb}} E (X_{\text{tot}} - X_{\text{p}}) X_{\text{p}} - k_{\text{off}} X_{\text{p}}.$$

Here k_{fb} and k_{off} are reaction constants.

We make one further simplifying assumption, namely, during the observations in the experiment, prior to X_{p} detection, the total amount X_{tot} of Parkin is much larger than the amount X_{p} on the mitochondria. Thus the amount X of free Parkin remains nearly

constant, approximately equal to the total amount X_{tot} of Parkin. We may therefore replace $X_{\text{tot}} - X_{\text{p}} = X$ by X_{tot}, which leads us to the differential equation

$$\frac{dX_{\text{p}}}{dt} = k_{\text{fb}} E X_{\text{tot}} X_{\text{p}} - k_{\text{off}} X_{\text{p}} = (k_{\text{fb}} E X_{\text{tot}} - k_{\text{off}}) X_{\text{p}}. \tag{10}$$

The coefficient $k_{\text{fb}} E X_{\text{tot}} - k_{\text{off}}$ is constant in time, so this differential equation is of the type $\frac{dx}{dt} = kx$, and its solution is given by the exponential growth formula $x(t) = e^{kt}x(0)$. In terms of X_{p} we get

$$X_{\text{p}}(t) = e^{(k_{\text{fb}} E X_{\text{tot}} - k_{\text{off}})t} X_{\text{p}}(0).$$

Indeed, equation (Eq. 10) is of the form (Eq. 5), if one lets $S(t)$ be the vector with only one component $S(t) = [X_{\text{p}}(t)]$, and if one lets $\mathcal{M}$ be the 1×1-matrix $\mathcal{M} = [k_{\text{fb}} E X_{\text{tot}} - k_{\text{off}}]$. The dominant (and only) eigenvalue of $\mathcal{M}$ is

$$\lambda_E = k_{\text{fb}} E X_{\text{tot}} - k_{\text{off}}.$$

However, since both the vector $S(t)$ and the matrix $\mathcal{M}$ only have one component, the eigenvalue analysis is not needed to solve the differential equation (Eq. 10) in this case.

In the experiment one begins with a given small amount $X_{\text{p}}(0)$ of Parkin and measures how long it takes before the amount $X_{\text{p}}(t)$ of Parkin reaches a fixed detectable level, $X_{\text{p,det}}$. By solving the equation $X_{\text{p}}(t) = X_{\text{p,det}}$ for t we find, as announced in (Eq. 2),

$$T_{\text{det}}(E) = \frac{\ln \frac{X_{\text{p,det}}}{X_{\text{p}}(0)}}{k_{\text{fb}} X_{\text{tot}} E - k_{\text{off}}} = \frac{\frac{1}{k_{\text{fb}} X_{\text{tot}}} \ln \frac{X_{\text{p,det}}}{X_{\text{p}}(0)}}{E - E_*} = \frac{C_*}{E - E_*}. \tag{11}$$

It follows from (Eq. 10) that the critical value of E, at which the systems "switches on", is

$$E_* = \frac{k_{\text{off}}}{k_{\text{fb}} X_{\text{tot}}},$$

while the constant C_* in the inverse law (Eq. 2) is given by

$$C_* = \frac{1}{k_{\text{fb}} X_{\text{tot}}} \ln \frac{X_{\text{p,det}}}{X_{\text{p}}(0)}.$$

The full model

The nonlinear model

Here we consider a more complete model for the PINK1-Parkin system. The full model is nonlinear, but by considering only the initial growth phase we can reduce the system to a linear set of differential equations. We then observe the existence of a dominant growth rate λ_{dom} and analyze its dependence on the parameters in the model.

The following variables appear in the full model

U_f, U_m, U_p**:** Three forms of Ubiquitin: free, mitochondrial, and phosphorylated
A_f, A_b, A_p**:** Three forms of Parkin: free, bound, and phosphorylated
E **:** The amount of PINK1 present in the system; a constant.

We assume that the system is governed by the following reactions (see model schematic in Fig. S5F-G):

$$U_f \underset{k_3}{\overset{k_1}{\rightleftarrows}} U_m \underset{k_5}{\overset{k_4 E}{\rightleftarrows}} U_p \underset{k_7}{\overset{k_6 A_f}{\rightleftarrows}} A_b \underset{k_9}{\overset{k_8 E}{\rightleftarrows}} A_p$$
$$U_f + A_p \xrightarrow{k_2} U_m + A_p$$

Assuming mass-action kinetics, the variables $U_f, U_m, U_p, A_f, A_m, A_p$ evolve according to the following set of differential equations

$$\begin{aligned}
\frac{dU_f}{dt} &= -k_1 U_f - k_2 U_f A_p + k_3 U_m \\
\frac{dU_m}{dt} &= k_1 U_f + k_2 U_f A_p - k_3 U_m - k_4 E U_m + k_5 U_p \\
\frac{dU_p}{dt} &= k_4 E U_m - k_5 U_p - k_6 U_p A_f + k_7 A_b \\
\frac{dA_f}{dt} &= -k_6 U_p A_f + k_7 A_b \\
\frac{dA_b}{dt} &= k_6 U_p A_f - k_7 A_b - k_8 E A_b + k_9 A_p \\
\frac{dA_p}{dt} &= k_8 E A_b - k_9 A_p
\end{aligned}$$

Linearization assuming abundant free Parkin and Ubiquitin

We can simplify the model by assuming that A_f and U_f are nearly constant because free Parkin and Ubiquitin are abundantly present. This leads to a reduced system with four components U_m, U_p, A_b, A_p, which satisfy the following four linear differential equations:

$$\begin{aligned}
\frac{dU_m}{dt} &= -(k_3 + k_4 E) U_m + k_5 U_p + k_2 U_f A_p \\
\frac{dU_p}{dt} &= k_4 E U_m - (k_5 + k_6 A_f) U_p + k_7 A_b \\
\frac{dA_b}{dt} &= + k_6 A_f U_p - (k_7 + k_8 E) A_b + k_9 A_p \\
\frac{dA_p}{dt} &= k_8 E A_b - k_9 A_p
\end{aligned} \tag{12}$$

This linear system is of the form $X'(t) = \mathcal{M} X(t)$ (see (Eq. 5)) where

$$X(t) = \begin{bmatrix} U_m \\ U_p \\ A_b \\ A_p \end{bmatrix}$$

The matrix in this linear system is

$$\mathcal{M} = \begin{bmatrix} -k_3 - k_4 E & k_5 & 0 & k_2 U_f \\ k_4 E & -k_5 - k_6 A_f & k_7 & 0 \\ 0 & k_6 A_f & -k_7 - k_8 E & k_9 \\ 0 & 0 & k_8 E & -k_9 \end{bmatrix}$$

Assuming all reaction rates k_i as well as the quantities E, A_f, U_f are positive, the matrix $\mathcal{M}$ satisfies the description on Eigenvalue Analysis surrounding (Eq. 6) in this appendix, i.e.

- the off-diagonal entries of $\mathcal{M}$ are non negative
- the matrix $\mathcal{M}$ is irreducible

This implies that $\mathcal{M}$ has a dominant eigenvalue λ_{dom} and corresponding left- and right-eigenvectors

$$W_{\text{dom}} = \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \end{pmatrix}, \qquad V_{\text{dom}} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}, \qquad \text{for which } \mathcal{M}^\top W_{\text{dom}} = \lambda_{\text{dom}} W_{\text{dom}}, \quad \mathcal{M} V_{\text{dom}} = \lambda_{\text{dom}} V_{\text{dom}} .$$

Lemma 1. *The dominant eigenvalue is a differentiable function of the parameters k_2, k_3, ..., k_9, as well as E, A_f, and U_f.*

Proof. This follows from the fact that the dominant eigenvalue is a simple eigenvalue, and that simple eigenvalues of any matrix are differentiable functions of the entries of the matrix $\mathcal{M}$. □

We will show that the dominant eigenvalue turns out to be a monotone function of the parameters, at least when $\lambda_{\text{dom}} \geq 0$. The following property of the left eigenvectors W_{dom} will help in the analysis of the derivatives of λ_{dom} with respect to the parameters.

Lemma 2. *If $\lambda_{\text{dom}} \geq 0$ and if the parameters k_2, k_3, ..., k_9, as well as E, A_f, and U_f are all positive, then the entries of the left eigenvector are increasing:*

$$w_1 < w_2 < w_3 < w_4. \tag{13}$$

Proof. Expanding the eigenvalue equation $\mathcal{M}^\top W_{\text{dom}} = \lambda_{\text{dom}} W_{\text{dom}}$ and rearranging terms we get

$$\begin{aligned} -k_3 w_1 + k_4 E(w_2 - w_1) &= \lambda_{\text{dom}} w_1 \\ k_5(w_1 - w_2) + k_6 A_f (w_3 - w_2) &= \lambda_{\text{dom}} w_2 \\ k_7(w_2 - w_3) + k_8 E(w_4 - w_3) &= \lambda_{\text{dom}} w_3 \\ k_2 U_f w_1 + k_9(w_3 - w_4) &= \lambda_{\text{dom}} w_4 \end{aligned}$$

Using the assumption that $\lambda_{\text{dom}} \geq 0$ we conclude from the first equation

$$k_4 E(w_2 - w_1) = \lambda_{\text{dom}} w_1 + k_3 w_1 \geq k_3 w_1 > 0 \implies w_2 - w_1 > 0.$$

The second equation then implies

$$k_6 A_f (w_3 - w_2) = \lambda_{\text{dom}} w_2 + k_5(w_2 - w_1) > 0 \implies w_3 - w_2 > 0.$$

Finally the third equation leads to

$$k_8 E(w_4 - w_3) = \lambda_{\text{dom}} w_3 + k_7(w_3 - w_2) > 0 \implies w_4 - w_3 > 0.$$

□

Lemma 3. *Let z be one of the parameters k_2, k_3, …, k_9, or E. If the left and right eigenvectors are normalized by $\langle W_{\text{dom}}, V_{\text{dom}} \rangle = 1$, then the derivative of λ_{dom} with respect to z is given by*

$$\frac{\partial \lambda_{\text{dom}}}{\partial z} = \left\langle W_{\text{dom}}, \frac{\partial \mathcal{M}}{\partial z} \cdot V_{\text{dom}} \right\rangle \tag{14}$$

Proof. Differentiate the relation $\mathcal{M} V_{\text{dom}} = \lambda_{\text{dom}} V_{\text{dom}}$ with respect to z to get

$$\mathcal{M} \frac{\partial V_{\text{dom}}}{\partial z} + \frac{\partial \mathcal{M}}{\partial z} \cdot V_{\text{dom}} = \lambda_{\text{dom}} \frac{\partial V_{\text{dom}}}{\partial z} + \frac{\partial \lambda_{\text{dom}}}{\partial z} V_{\text{dom}}$$

Take the inner product with W_{dom} on both sides:

$$\left\langle W_{\text{dom}}, \mathcal{M} \frac{\partial V_{\text{dom}}}{\partial z} \right\rangle + \left\langle W_{\text{dom}}, \frac{\partial \mathcal{M}}{\partial z} \cdot V_{\text{dom}} \right\rangle = \left\langle W_{\text{dom}}, \lambda_{\text{dom}} \frac{\partial V_{\text{dom}}}{\partial z} \right\rangle + \frac{\partial \lambda_{\text{dom}}}{\partial z} \langle W_{\text{dom}}, V_{\text{dom}} \rangle.$$

Since W_{dom} is a left eigenvector, this implies

$$\lambda_{\text{dom}} \left\langle W_{\text{dom}}, \frac{\partial V_{\text{dom}}}{\partial z} \right\rangle + \left\langle W_{\text{dom}}, \frac{\partial \mathcal{M}}{\partial z} \cdot V_{\text{dom}} \right\rangle = \lambda_{\text{dom}} \left\langle W_{\text{dom}}, \frac{\partial V_{\text{dom}}}{\partial z} \right\rangle + \frac{\partial \lambda_{\text{dom}}}{\partial z} \langle W_{\text{dom}}, V_{\text{dom}} \rangle.$$

Cancelling the first terms on both sides and then using $\langle W_{\text{dom}}, V_{\text{dom}} \rangle = 1$ leads to (Eq. 14).
□

Lemma 4. *As long as the dominant eigenvalue λ_{dom} is nonnegative, it is an increasing function of k_2, k_4, k_6, k_8 (forward reactions), and E, while it is a decreasing function of k_3, k_5, and k_7 (reverse reactions).*

Proof. Using the previous Lemma we can compute the derivative of λ_{dom} with respect to any of the parameters. Lemma 2 then tells us the sign of the derivative. Computing this for each of the parameters leads to the following result:

z	$\frac{\partial \lambda_{\text{dom}}}{\partial z} = \langle W_{\text{dom}}, \frac{\partial \mathcal{M}}{\partial z} V_{\text{dom}} \rangle$		
k_2	$U_f w_1 v_4 > 0$	increasing	always
k_3	$-w_1 v_1 < 0$	decreasing	always
k_4	$E v_1 (w_2 - w_1) > 0$	increasing	if $\lambda_{\text{dom}} \geq 0$
k_6	$A_f v_2 (w_3 - w_2) > 0$	increasing	if $\lambda_{\text{dom}} \geq 0$
k_8	$E v_3 (w_4 - w_3) > 0$	increasing	if $\lambda_{\text{dom}} \geq 0$
E	$k_4 v_1 (w_2 - w_1) + v_3 k_8 (w_4 - w_3) > 0$	increasing	if $\lambda_{\text{dom}} \geq 0$
k_5	$v_2 (w_1 - w_2) < 0$	decreasing	if $\lambda_{\text{dom}} \geq 0$
k_7	$v_3 (w_2 - w_3) < 0$	decreasing	if $\lambda_{\text{dom}} \geq 0$

□

The critical PINK1 value E_*

Under the assumption that the parameters k_2, k_3, ..., k_9, U_f, and A_f are positive we will argue that there is a critical value E_* such that $\lambda_{\rm dom} > 0$ for $E > E_*$ and $\lambda_{\rm dom} < 0$ for $E < E_*$. Moreover we analyze how E_* changes if one of the parameters k_2, k_3, ..., k_9, U_f, A_f is changed.

Lemma 5. *When $E = 0$, one has $\lambda_{\rm dom} < 0$, while for $E \to \infty$ the dominant eigenvalue converges to a positive limiting value $\lambda_{\rm dom}^{\infty} > 0$. In fact there is a constant Λ_∞ such that*

$$\lambda(E) = \lambda_\infty - \frac{\Lambda_\infty}{E} + \mathcal{O}\Big(\frac{1}{E^2}\Big) \qquad (E \to \infty) \tag{15}$$

Proof. We postpone the rather long proof to the next section. □

Lemma 6. *There is a unique positive number E_* such that $\lambda_{E_*} = 0$. For all $E > E_*$ one has $\lambda_{\rm dom} > 0$, while for $0 < E < E_*$ one has $\lambda_{\rm dom} < 0$.*

Proof. We have just shown that $\lambda_{\rm dom} < 0$ when $E = 0$, while $\lambda_{\rm dom} > 0$ for large E. It follows from continuous dependence of the dominant eigenvalue on all parameters that there must exist intermediate values E_* at which $\lambda_{\rm dom}$ vanishes. In Lemma 4 we showed that whenever $\lambda_{\rm dom} = 0$, $\lambda_{\rm dom}$ is increasing. This implies that there cannot be more than one E_* at which $\lambda_{\rm dom}$ vanishes. □

Lemma 7. *The critical PINK1 level E_* is an increasing function of k_3, k_5, k_7, and a decreasing function of k_2, k_4, k_6, and k_8.*

Proof. By implicit differentiation applied to the equation $\lambda_{\rm dom}(z, E_*) = 0$ we find that

$$\frac{\partial E_*}{\partial z} = -\frac{\partial \lambda_{\rm dom}/\partial z}{\partial \lambda_{\rm dom}/\partial E}.$$

The Lemma now follows from the table in Lemma 4. □

Proofs of Lemma 5

We can write the matrix $\mathcal{M}$ as

$$\mathcal{M} = \mathcal{M}_0 + E\mathcal{M}_1$$

where

$$\mathcal{M}_0 = \begin{bmatrix} -k_3 & k_5 & 0 & k_2U_f \\ 0 & -k_5 - k_6A_f & k_7 & 0 \\ 0 & k_6A_f & -k_7 & k_9 \\ 0 & 0 & 0 & -k_9 \end{bmatrix} \qquad \mathcal{M}_1 = \begin{bmatrix} -k_4 & 0 & 0 & 0 \\ k_4 & 0 & 0 & 0 \\ 0 & 0 & -k_8 & 0 \\ 0 & 0 & k_8 & 0 \end{bmatrix}$$

The dominant eigenvalue of $\mathcal{M}$ is the largest real root λ of the characteristic equation

$$\begin{vmatrix} -k_3 - k_4E - \lambda & k_5 & 0 & k_2U_f \\ k_4E & -k_5 - k_6A_f - \lambda & k_7 & 0 \\ 0 & k_6A_f & -k_7 - k_8E - \lambda & k_9 \\ 0 & 0 & k_8E & -k_9 - \lambda \end{vmatrix} = 0.$$

Proof of Lemma 5 when $E = 0$

We compute the characteristic polynomial for $E = 0$:

$$\begin{aligned}\det(\mathcal{M} - \lambda) &= \det(\mathcal{M}_0 - \lambda) \\ &= \begin{vmatrix} -k_3 - \lambda & k_5 & 0 & k_2 U_f \\ 0 & -k_5 - k_6 A_f - \lambda & k_7 & 0 \\ 0 & k_6 A_f & -k_7 - \lambda & k_9 \\ 0 & 0 & 0 & -k_9 - \lambda \end{vmatrix} \\ &= (\lambda + k_3)(\lambda + k_9)\big(\lambda^2 + (k_5 + k_7 + k_6 A_f)\lambda + k_5 k_7\big)\end{aligned}$$

It follows that when $E = 0$ the eigenvalues of the matrix $\mathcal{M}$ are

$$\lambda_1 = -k_3, \quad \lambda_2 = -k_9,$$
$$\lambda_3, \lambda_4 = \frac{-k_5 - k_7 - k_6 A_f \pm \sqrt{(k_5 - k_7)^2 + 2(k_5 + k_7)k_6 A_f + (k_6 A_f)^2}}{2}$$

All four eigenvalues are real and negative. The dominant eigenvalue λ_{dom} is the largest of these,

$$\lambda_{\text{dom}} = \max\{\lambda_1, \lambda_2, \lambda_3, \lambda_4\} \text{ if } E = 0$$

and it follows that for $E = 0$ one has $\lambda_{\text{dom}} < 0$.

Proof of Lemma 5 for large E

We write the characteristic polynomial as

$$\det(\mathcal{M} - \lambda) = D_0(\lambda) + D_1(\lambda)E + D_2(\lambda)E^2 \tag{16}$$

where D_0, D_1, D_2 are polynomials in λ, which upon computation turn out to satisfy

$$\begin{aligned}D_0(\lambda) &= \det(\mathcal{M}_0 - \lambda) \\ &= (k_3 + \lambda)(k_9 + \lambda)\big(\lambda^2 + (k_5 + k_7 + k_6 A_f)\lambda + k_5 k_7\big) \\ &= \lambda^4 + \text{lower order terms},\end{aligned}$$

$$\begin{aligned}D_1(\lambda) &= \lambda\Big(k_4(\lambda + k_6 A_f + k_7)(\lambda + k_9) + (\lambda + k_3)(k_8\lambda + k_5 k_8 + (k_8 - k_7)k_7 A_f)\Big) \\ &= (k_4 + k_8)\lambda^3 + \big[k_4(k_7 + k_9) + (k_3 + k_5)k_8 + (k_4 + k_8 - k_7)k_6 A_f\big]\lambda^2 \\ &\quad + (k_3 k_5 k_8 + k_3(k_8 - k_7)k_6 A_f)\lambda \\ &= (k_4 + k_8)\lambda^3 + \text{lower order terms},\end{aligned}$$

and

$$\begin{aligned}D_2(\lambda) &= k_4 k_8(\lambda^2 + k_6 A_f \lambda - k_2 U_f k_6 A_f) \\ &= k_4 k_8 \lambda^2 + \text{lower order terms}\end{aligned}$$

For large values of E the four eigenvalues of $\mathcal{M}$ can be separated into those eigenvalues λ for which $\lambda \ll E$, and those for which λ is comparable to E or larger.

If $|\lambda| \sim E$ or $|\lambda| \gg E$ then the dominant terms in the characteristic polynomial (Eq. 16) are those that contain $\lambda^4, \lambda^3 E, \lambda^2 E^2$. Two eigenvalues are therefore approximated by the nonzero roots of

$$\lambda^4 + (k_4 + k_8)\lambda^3 E + k_4 k_8 \lambda^2 E^2 = 0.$$

This yields two very negative eigenvalues

$$\lambda_1 \approx -k_4 E, \quad \lambda_2 \approx -k_8 E.$$

If on the other hand $|\lambda| \ll E$ then $D_2(\lambda)E^2$ is the dominant term in the characteristic polynomial (Eq. 16), and thus two of the eigenvalues are close to the roots of $D_2(\lambda) = 0$, i.e. $\lambda^2 + k_6 A_f \lambda - k_2 U_f k_6 A_f = 0$, which are given by

$$\lambda_{\pm}^{\infty} = \frac{-k_6 A_f \pm \sqrt{(k_6 A_f)^2 + 4 k_2 U_f k_6 A_f}}{2}.$$

Of these, λ_{-}^{∞} is negative and $\lambda_{\text{dom}}^{\infty}$ is positive. Since $\lambda_{\text{dom}}^{\infty}$ is the only positive eigenvalue, it is the dominant eigenvalue.

The dominant eigenvalue therefore satisfies

$$\lambda_{\text{dom}} \approx \lambda_{\text{dom}}^{\infty} = \frac{-k_6 A_f + \sqrt{(k_6 A_f)^2 + 4 k_2 U_f k_6 A_f}}{2} > 0. \tag{17}$$

Thus we have shown that the dominant eigenvalue does indeed converge to the limiting value λ_∞. To complete the proof of Lemma 5 we now verify the asymptotic formula (Eq. 17). We can do this by recalling that λ is a solution of the characteristic equation

$$\det(\mathcal{M} - \lambda) = 0$$

which we can rewrite using (Eq. 16) as

$$D_0(\lambda) + D_1(\lambda)E + D_2(\lambda)E^2 = 0.$$

Divide both sides by E^2 to get

$$D_2(\lambda) + D_1(\lambda)E^{-1} + D_0(\lambda)E^{-2} = 0.$$

Instead of regarding this as an equation for λ and E, we introduce a new variable

$$\epsilon = \frac{1}{E}$$

which is related to λ by

$$D_2(\lambda) + D_1(\lambda)\epsilon + D_0(\lambda)\epsilon^2 = 0. \tag{18}$$

Abbreviate the left hand side in this equation to $\varphi(\lambda, \epsilon) = D_2(\lambda) + D_1(\lambda)\epsilon + D_0(\lambda)\epsilon^2$. The limiting value λ_∞ is a solution of $D_2(\lambda_\infty) = 0$, so $\varphi(\lambda_\infty, 0) = 0$. Since λ_∞ is the largest root of the quadratic polynomial $D_2(\lambda)$ we have $D_2'(\lambda_\infty) > 0$. This implies

$$\frac{\partial \varphi}{\partial \lambda}(\lambda_\infty, 0) = D_2'(\lambda_\infty) \neq 0, \quad \text{and} \quad \frac{\partial \varphi}{\partial \epsilon}(\lambda_\infty, 0) = D_1(\lambda_\infty),$$

and we may therefore invoke the implicit function theorem to conclude that the solution $\lambda(\epsilon)$ of $\varphi(\lambda, \epsilon) = 0$ is a smooth function of ϵ. Its Taylor expansion begins with

$$\lambda = \lambda_\infty - \frac{D_1(\lambda_\infty)}{D_2'(\lambda_\infty)}\epsilon + \mathcal{O}(\epsilon^2).$$

Finally, after setting $\epsilon = \frac{1}{E}$, we obtain (Eq. 15), where the constant Λ_∞ is given by

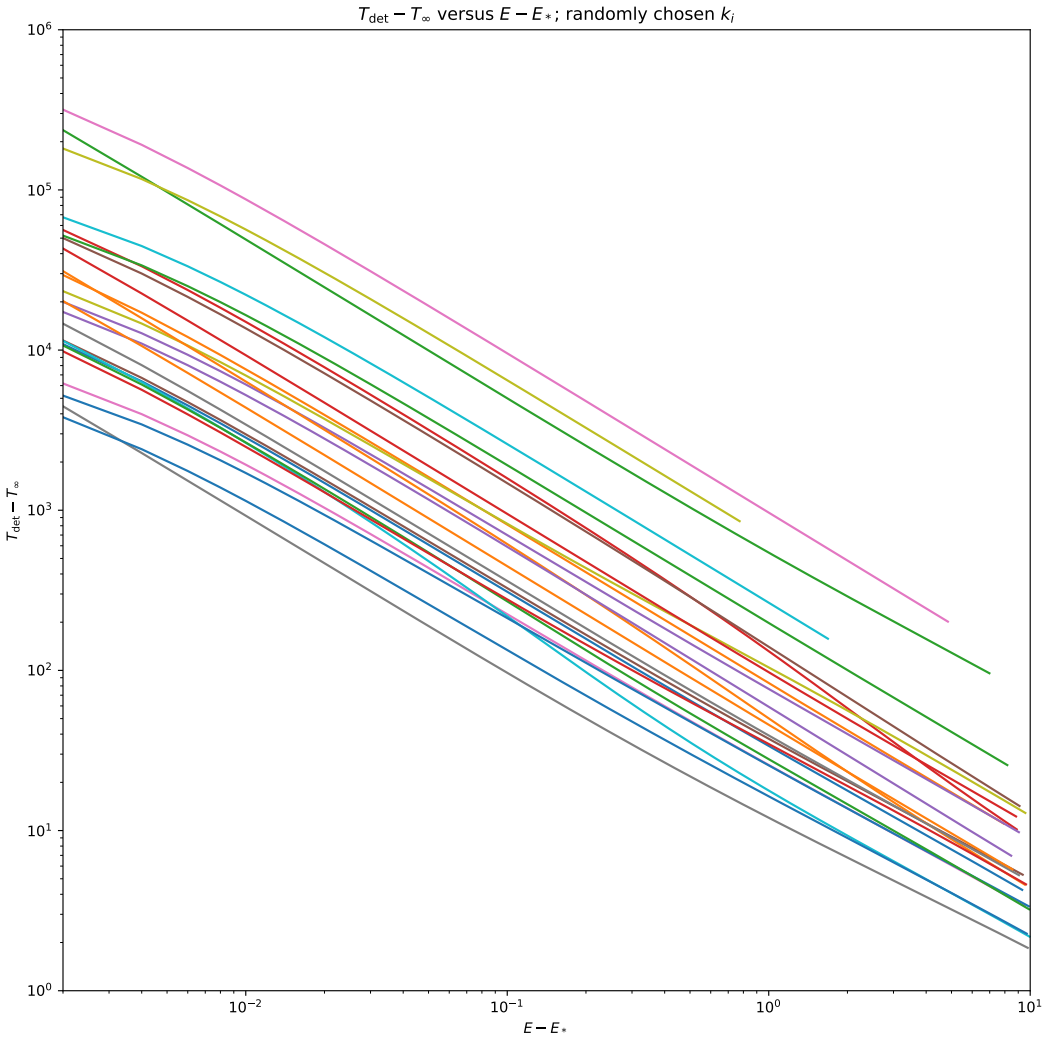
$$\Lambda_\infty = \frac{D_1(\lambda_\infty)}{D_2'(\lambda_\infty)}.$$

Numerical computation of T_{det}

While there is no explicit formula that expresses the largest eigenvalue λ_∞ of the matrix $\mathcal{M}(E)$, and thus also the time to detection T_{det}, in terms of E and the parameters $k_1, \ldots, k_9, U_f, A_f$ both λ_∞ and T_{det} can be easily computed numerically for any specific given values of the parameters.

Using the `eigvals` routine from the Numpy.linalg package we produced log-log plots of $T_{\text{det}} - T_\infty$ vs. $E - E_*$. See Appendix Figure 1. In these plots the parameters $k_1, \ldots, k_9$ were chosen using a random number generator so that $\log k_i$ is uniformly distributed with $-1 \leq \log k_i \leq +1$. After choosing the parameters k_i we normalized their product, so that $k_1 k_2 \cdots k_8 k_9 = 1$.

One sees from the simulations that plotting a log-log graph of $T_{\text{det}} - T_\infty$ vs. $E - E_*$ consistently produces a nearly straight line with slope approximately equal to -1. This implies that the dependence of T_{det} on E follows the inverse law (Eq. 2).



APPENDIX FIGURE 1. $T_{\text{det}} - T_\infty$ vs $E - E_*$ for randomly chosen parameter values $k_1, \ldots, k_9$