Introduction to Computational Systems Biology

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The Holy Grail

Theory

A Whole-Cell Computational Model **Predicts Phenotype from Genotype**

Jonathan R. Karr, ^{1,4} Jayodita C. Sanghvi,^{2,4} Derek N. Macklin,² Miriam V. Gutschow,² Jared M. Jacobs,² Benjamin Bolival, Jr.,² Nacyra Assad-Garcia,³ John I. Glass,³ and Markus W. Covert^{2,*} ¹Graduate Program in Biophysics ²Department of Bioengineering Stanford University, Stanford, CA 94305, USA ³J. Craig Venter Institute, Rockville, MD 20850, USA ⁴These authors contributed equally to this work *Correspondence: mcovert@stanford.edu http://dx.doi.org/10.1016/j.cell.2012.05.044

Mycobacterium with 600 genes. Scaling to Eucaryotes is highly non-trivial.

Biological systems

A cell is made of many subsystems, performing different tasks and interacting among them.

We have several *classes* of subsystems

sensor networks signalling networks gene networks transport networks metabolic networks

…

Most biological systems can be described as a set of bio-chemical reactions, to be intended as a modelling language.

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 $gene \longrightarrow_{kp} gene + mrna$ $mra \longrightarrow_{kt} mrna + protein$ protein + protein \longrightarrow_{k1} dimer $dimer \longrightarrow_{k0}$ protein + protein $dimer + gene \rightarrow_{kb} gene_repr$ gene_repr —>ku dimer + gene

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 $d[S]/dt$ = -k1[S][E] + k0[ES] $d[E]/dt$ = -k1[S][E] + k0[ES] +k[ES] $d[ES]/dt = -k[ES] - k0[ES] + k1[S][E]$ $d[P]/dt = k[ES]$ [S] P1 Concentration $[E]$

Time

ES

Under time-scale separation, we can assume $d[ES]/dt = 0$, getting the classic Michaelis Menten kinetics:

Cooperation/competition between enzyme and substrate results in the Hill kinetics: $d[P]/dt=V_{max} [S]^{n}/(K^{n} + [S]^{n})$

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Proc. Natl. Acad. Sci. USA Vol. 93, pp. 10078-10083, September 1996 Biochemistry

Ultrasensitivity in the mitogen-activated protein kinase cascade

CHI-YING F. HUANG AND JAMES E. FERRELL, JR.[†]

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Ultrasensitivity in the mitogen-activated protein kinase cascade

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input stimulus ($E1_{\text{tot}}$ in multiples of the EC50)

Negative feedback and ultrasensitivity can bring about oscillations in the the state of the state of \sim mitogen-activated protein kinase cascades Ras/MKKKK

Boris N. Kholodenko

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA

Signal transduction networks membrane-bound GTPase Ras. SOS catalyzes the conversion of Riamal transal state. Rassisten kinase of the MAPK cascade by recruiting Raf to the plasma correspond to the total concentrations of MKKK, MKK and MAPK (Table 1).

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Boris N. Kholodenko \blacksquare interventing \blacksquare

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MAPK cascade. Table 1. Kinetic equations comprising the computational model of the $\mathbf{E}_{\mathbf{G}}$

 $s_{\rm eff}$ promotes the activation of $R_{\rm eff}$ promotes the activation of $R_{\rm eff}$

was the general emerging property of phosphorylation property of p

 $d[MKKK]/dt = v_2-v_1$ $d[MKKK-P]/dt = v_1-v_2$ $r_1 r_2$
in the sensitivity of the target to the target to the signal: $d[MKK]/dt = v_6-v_3$ $d[MKK-P]/dt = v_3 + v_5 - v_4 - v_6$ $d[MKK-PP]/dt = v_4 - v_5$ $d[MAPK]/dt = v_{10}-v_7$ $\frac{16}{\text{d}}$ MAPK-P1/dt = $v_a + v_b - v_a - v_a$. $c_1 = c_2 = c_3$. $d[MAPK-PP]/dt = v_8 - v_9$ Moiety conservation relations: $[MKKK]_{\text{total}} = [MKKK] + [MKKK-P]$ $[MKK]_{\text{total}} = [MKK] + [MKK-P] + [MKK-PP]$ t^{MIMM} found to t^{MIMM} and t^{MIMM} and t^{MAMM} $[NIAT\ N_{total} - [NIAT\ N] + [NIAT\ N^T]$ v_2 - v_1 \mathbf{v} -V₂ $\frac{1}{\sqrt{2}}$ $d[MKK-P]/dt = v_3 + v_5 - v_4 - v_6$ V_{10} e V_{7} d[MAPK-P]/dt $= v_7 + v_9 - v_8 - v_{10}$ Moiety conservation relations: $\begin{bmatrix} 1 & 1 \end{bmatrix}$ is an order property of the MAPK cases of the MAPK cases $[MAPK]_{total} = [MAPK] + [MAPK-P] + [MAPK-PP]$

eggs, and the signal transfer from MKK (MEK1) to p42 MAPK (MEK1) to p42 MAPK (MEK1) to p42 MAPK (MEK1) to p42 M

Mos results in the activation of p42 MAPK, but in turn, p42

$1₀$

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90% of the total kinase concentrations were tested).

 Ras/MKKKK mechanism. Monophosphorylated products are released into \blacklozenge \downarrow molecule $[1, 7]$. Because only biphosphorylated kinases are functions are functi active in the multiplier of the multiplier protein terms of the phosphatases protein the phosphatases of the p
Separate phosphatases in the phosphatases of the phosphatases in the phosphatases of the phosphatases in the p \sim 2 \sim 1 inactivate the MAPK cascade kinases. Table 2 presents the rate expressions of the MAPK cases of the total matrix of the MAPK cases of the MAPK cases of the MAPK cases of the MAPK cases of the MA $\sqrt{3}$ MKK and MAPK were reported to $\sqrt{4}$ be in the range in the method is less than $MKK-PP$ \sim 6 \sim 5 \sim 1 and the Km values of λ be in the same range \sim $\sqrt{2}$ 8 $1/2$ space $1/2$ map $1/2$ map **MAPK-PP** \overline{Q}

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MAPK cascade. Table 1. Kinetic equations comprising the computational model of the $\mathbf{E}_{\mathbf{G}}$ increase in MAPK-PP. As the phosphatase continues to operate

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\frac{1}{2} \text{Var} \times \frac{1}{2} \text{Var} \times \frac{1}{2} \text{Var} \times \frac{1}{2} \\
\frac{1}{2} \text{Var} \times \frac{1}{2} \end{aligned}\n\end{aligned}\n\$ $\begin{array}{ccc} \text{if } & \text{$ $d[MAPK-PP]/dt = v_8 - v_9$ $\begin{bmatrix} 1 \\ 1 \end{bmatrix}$ Moiety conservation relations: $\begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$ [MKKK]_{total} = [MKKK] + [MKKK-*P*] $\mathcal{U}\setminus\mathcal{U}$ [MKK]_{total} = [MKK] + [MKK-P] + [MKK-PP] $[MAX1] \begin{bmatrix} \text{P} \end{bmatrix} \begin{bmatrix} \text{P} \end{bmatrix} + [MIN1] \begin{bmatrix} \text{P} \end{bmatrix} \begin{bmatrix} \text{P} \end{bmatrix}$ $[IMAT\ N]_{total} = [MAT\ N] + [NIAT\ N^T]$ v_2 - v_1 \mathbf{v} -V₂ $\frac{1}{\sqrt{2}}$ $d[MKK-P]/dt = v_3 + v_5 - v_4 - v_6$ V_{10} e V_{7} $d[MAPK-P]/dt = v_7 + v_9 - v_8 - v_{10}$ μ ion relations. $\begin{bmatrix} 1 & 1 \end{bmatrix}$ is an order property of the MAPK cases of the MAPK cases $[MAPK]_{total} = [MAPK] + [MAPK-P] + [MAPK-P]$ was the general emerging property of phosphorylation property of p μ_{UVININ} and μ_{UVIN} rate and the concentration of concentra $d[MKKK-P]/dt = v_1-v_2$ Moiety conservation relations: $\frac{1}{2}$ in a set of kinetic parameters and $\frac{1}{2}$ in $\frac{1}{2$ $[MKKK]_{\text{total}} = [MKKK] + [MKKK-P]$ 90% of the total kinase concentrations were tested). $d[MKKK]/dt = v_2-v_1$

parameters (Table 1). The cascade kinases did not remain

Genetic Networks

Genetic regulatory networks describe the complex regulation of gene expression, which is the "software of life"

Ubig-ubiguitous: Mat - maternal: activ - activator; rep - repressor; unkn = unknown; Nucl. = nuclearization; g = \$-catenin source; eβ-TCF = nuclearized b-β-catenin-Tcf1; E5 = early signal;

ECNS - early cytoplasmic nuclearization system; Zyq. N. = zyqotic Notch

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Genetic Networks

A typical example of genetic regulatory network is the circadian clock (here in cyanobacteria, peculiar), an oscillatory module regulated by alternation of light and dark.

Hertel et al. 2013 model simulation — kaiA_mRNA — kaiBC_mRNA — KaiA — KaiC6_U — KaiC6_T — KaiC6_S — KaiC6_D — KaiBC_U $-$ KaiBC S $-$ KaiBC D $-$ KaiC U $-$ KaiC T $-$ KaiC S $-$ KaiC D KaiBC T Hide all 3.5 -3 2.5 \overline{z} 1.5 $\mathbf{1}$ 0.5 -0.5 -00 $\sqrt{5}$ 0ءِ, ø Time Highcharts.com Change axis type Fit to scale Edited by Petr Horáček

Revealing a Two-Loop Transcriptional Feedback Mechanism in the Cyanobacterial Circadian Clock

Stefanie Hertel [5], Christian Brettschneider, Ilka M. Axmann

Published: March 14, 2013 . http://dx.doi.org/10.1371/journal.pcbi.1002966

A Noisy Life

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A Noisy Life

Science

A AAAS

Molecular interactions and gene expression in single cells are **random events**, the fewer the molecules involved, the more the effect of **noise**.

Models have to account for this.

Fig. 2. Noise in E. coli. CFP and YFP fluorescence images were combined in the green and red channels, respectively. (A) In strain RP22, with promoters repressed by the wild-type lacl gene, red and green indicate significant amounts of intrinsic noise. (B) RP22 grown in the presence of lac inducer, 2 mM IPTG. Both fluorescent proteins are expressed at higher levels and the cells exhibit less noise. (C) As in (B), except the recA gene has been deleted, increasing intrinsic noise. (D) Another wild-type strain, MG22, shows noise characteristics similar to those of RP22. (E) Expression levels and noise in unrepressed lach strain M22 are similar to those in lacl⁺ strains induced with IPTG (B). (F) M22 cells regulated by the Repressilator (16), an oscillatory network that amplifies intrinsic noise.

A Noisy Life

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Michael B. Elowitz, et al. Science 297, 1183 (2002); DOI: 10.1126/science.1070

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What are the **sources of noise** in cells?

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Intrinsic and extrinsic contributions to stochasticity in gene expression

Peter S. Swain*¹¹, Michael B. Elowitz*⁵, and Eric D. Siggia*

What is **the role of noise** in cells? Is it a nuisance to cope with, or it has also been exploited by Nature?

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Stochasticity and Cell Fate Richard Losick and Claude Desplan Science 320, 65 (2008);
DOI: 10.1126/science.1147888

Fig. 1. Stochastic distribution of cell fates in bacteria and in insect photoreceptors. (A) Fluorescence micrograph of B , subtilis cells containing the coding sequence for GFP fused to the promoter for a gene under the control of the competence requlator ComK. The cells were visualized with a red stain; the green fluorescence reveals the subpopulation of cells that are ON for ComK. The cells are 1 to 2 um in length. (B) Photograph of a whole adult Drosophila retina whose R8 photoreceptors were stained with antibodies to the green-sensitive photopigment Rh6 (green) and the blue-sensitive photopigment Rh5 (blue). The horizontal distance between photoreceptors is about 10 µm .

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REVIEW

Strategies for cellular decision-making

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Mechanisms of noise-resistance in genetic oscillators

Vilar*[†], Hao Yuan Kueh*, Naama Barkai[‡], and Stanislas Leibler*^{†§}

 $dD_A/dt = \theta_A D'_A - \gamma_A D_A A$ $dD_R/dt = \theta_R D_R' - \gamma_R D_R A$ $dD'_{A}/dt = \gamma_{A}D_{A}A - \theta_{A}D'_{A}$ $dD'_{R}/dt = \gamma_{R}D_{R}A - \theta_{R}D'_{R}$ $dM_A/dt = \alpha'_A D'_A + \alpha_A D_A - \delta_M M_A$ $dM_A/dt = \alpha'_A D'_A + \alpha_A D_A - \delta_{M_A} M_A$ $dA/dt = R.M + A.D' + A.D'$ $dA/dt = \beta_A M_A + \theta_A D'_A + \theta_R D'_R$ $A(\gamma D + \gamma D + \gamma D + \gamma E + \delta)$ $- A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A)$ is assumed to be the unity so that concentrations and number of \mathbb{R}^n and number of \mathbb{R}^n $dM_R/dt = \alpha'_R D'_R + \alpha_R D_R - \delta_{M_R} M_R$ $\mathbf{A} \mathbf{A} \mathbf{A}$ $dR/dt = \beta_R M_R - \gamma_C AR + \delta_A C - \delta_R R$ $dC/dt = \gamma_C AR - \delta_A C$

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Mechanisms of noise-resistance in genetic oscillators

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Mechanisms of noise-resistance in genetic oscillators

fixed point (*R*0,*C*0). When approaching the fixed point, *R˙* destabilising effect: sending it back upwards to initiate a new cycle. T MAKES OSCIIIATIONS it makes oscillations sponding to the slow degradation of *R*. These two distinct phases are characteristic of excitable systems, the classic example of persistent transmission in neurons (9, 10). The fast and slow legs correngar critical noints near critical points. point (*R*0,*C*0) and hits the *R˙* " 0 nullcline on the left to begin the versions of the model. The values of the parameters are as in the caption of Fig. 1, R *B and that now we set a part of the set in a* Noise can have a

Chemical Reaction Networks can be modelled as **Markov Population Processes**. Variables count the amount of molecules per each species. Update vectors are defined by reactions. Rates depend on the total population (mass action, Hill).

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 $mra \longrightarrow_{kt} mrna + protein$

protein + protein \longrightarrow_{k1} dimer

 $dimer \longrightarrow_{k0}$ protein + protein

dimer + gene ->kb gene_repr gene_repr \longrightarrow_{ku} dimer + gene

Counting variables:

xgene, xgene_repr, xmrna, xprotein, xdimer **Propensity of a reaction** (expected frequency) follows the mass action law:

 $a_1(\mathbf{x}) = k_p$ x_{gene} ; $a_5(\mathbf{x}) = k_p$ x_{dimer} x_{gene} ;

$$
a_3(\mathbf{x}) = k_1 \times_{\text{protein}} (x_{\text{protein}} - 1)/2;
$$

Update of a reaction: net variation of each species **v₁** = $(0,0,1,0,0)$, **v₃** = $(0,0,0,-2,1)$, **v₅** = $(-1,1,0,0,-1)$

Chemical Reaction Networks can be modelled as **Markov Population Processes**. Variables count the amount of molecules per each species. Update vectors are defined by reactions. Rates depend on the total population (mass action, Hill).

 $gene \longrightarrow_{kp} gene + mrna$ $mra \rightarrow_{kt} mrna + protein$ protein + protein \longrightarrow_{k1} dimer $dimer \longrightarrow_{k0}$ protein + protein d imer + gene \rightarrow _{kb} gene_repr gene_repr \longrightarrow_{ku} dimer + gene

Counting variables:

xgene, xgene_repr, xmrna, xprotein, xdimer **Propensity of a reaction** (expected frequency) follows the mass action law:

 $a_1(\mathbf{x}) = k_p$ x_{gene} ; $a_5(\mathbf{x}) = k_p$ x_{dimer} x_{gene} ;

$$
a_3(\mathbf{x}) = k_1 \times_{\text{protein}} (x_{\text{protein}} - 1)/2;
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Update of a reaction: net variation of each species **v₁** = $(0,0,1,0,0)$, **v₃** = $(0,0,0,-2,1)$, **v₅** = $(-1,1,0,0,-1)$

Typical rate functions

- **Mass Action**: rate proportional to concentration/ numbers. The only one having a physical interpretation.
- **Hill Kinetics**. Typically used for enzymatic reactions or to implicitly model gene expression.

Rates and Scaling

Biochemical reactions happen in a volume V. We can convert molecule numbers into concentrations (often micro or nano-molar) dividing by V.

Molecule numbers: variables X count the number of molecules. Updates are integers. *Concentrations*: variable x are concentrations. Updates are multiple of 1/V.

How do rates change while passing from numbers to concentrations?

Example: dimerisation (P monomer, P_2 dimer)

Rates and Scaling

If we express the model in terms of concentrations, by multiplying rate and update vector of each transition and adding them up, we obtain the standard deterministic model of chemical kinetic, as a set of ODEs, the **reaction rate equations**.

Example: dimerisation.

Relation between stochastic and deterministic rate constants.

Example: gene networks

Self repressing gene module

Bistable switch

Example: gene networks

Repressilator

Feed Forward Loops

What about data?

Most of classic modelling approaches in systems biology (5-20 years ago) make a **limited use of data**, mostly because there was not much usable data available back then.

Kinetic rates were inferred from dedicated experiments (in vitro) and by exploration of biological literature to make educated guesses. This is a painstakingly time consuming and error prone process, impossible for large models.

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With the data revolution we are living in, more and more experimental techniques are capable of producing data that is good to fit dynamic models.

Typically, one needs **time series data.**

Examples of such technologies are flow cytometry, RNAsec, imaging techniques…

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The Plant Journal (2011) 66, 375-385

doi: 10.1111/j.1365-313X.2011.04489.x

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ODE model with 7 variables/ species

Data: luciferase time series, both transcriptional (LUC attached to CCA1 and TOC1), and translational (LUC attached to promoters of CCA1 and TOC1),

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Systems blology

Advance Access publication February 19, 9013

Hybrid regulatory models: a statistically tractable approach to model regulatory network dynamics Andrea Ocone¹, Andrew J. Millar^{8,8} and Guido Sanguinetti^{1,8,6}

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Systems blokeov

Hybrid regulatory models: a statistically tractable approach to model regulatory network dynamics

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A switching diffusion stochastic model (2 species) can predict behaviour more accurately.

New protein required to correctly capture the behaviour of both transcriptional and translational data.

Take home messages

Modelling can help **elucidating the role and functioning** of cellular components.

Multi scale modelling can deal with tissues, organs, and so on. It also tests if current knowledge is **consistent**.

Modelling large scale systems (e.g. whole cell) can provide a cheap **in silico experimentation environment** (e.g. for drug testing)

Modelling is a **key enabling technology** in **synthetic biology**: it allows cheap and fast exploration of the design space.

Modelling requires **time-series data** to estimate model parameters. High quality data is required for proper model identification.