Fragility of Stochastic Dynamics in Autocatalytic Reaction Networks (of Togashi-Kaneko type)

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Based on joint work with:
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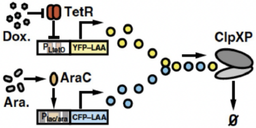
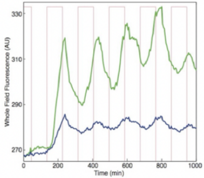
Stochastic Dynamics in Molecular and Cellular Biology



Coupled Enzymatic Processing

(Hasty-Tsimring UCSD lab)

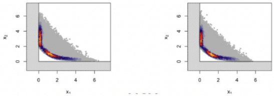


$$\emptyset \underset{\kappa_1}{\overset{\kappa_2}{\rightleftharpoons}} S_1 \xrightarrow{\kappa_5} S_2 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} \emptyset$$

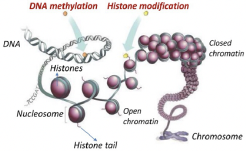
$$2S_1 + S_2 \xrightarrow{\kappa_6} 3S_1$$

Diffusion Approximations

(with boundary reflection)

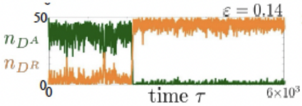


MC **CLA**



Epigenetic Cell Memory

(Del Vecchio-Weiss MIT lab)



Autocatalysis in Cancer

Autocatalytic reactions of the form

$$A + B \to 2B$$

can drive aggressive progression or treatment therapies

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Some Examples

- Autocatalytic polymerization of the cytoskeletal actin network
- Self-replicating colorectal tissue growth
- Engineered nanotechnology to destroy cancer cells

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Features

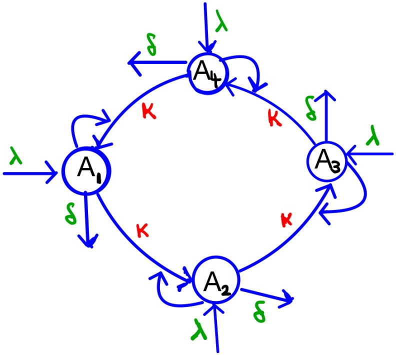
- Nonlinear dynamics with positive feedback loops
- Bistability, oscillations and switching between tumor proliferation and suppression
- Stochastic fluctuations can push a system to switch between healthy and malignant states

Togashi-Kaneko model

Togashi-Kaneko (Phys.Rev.E 2001): cycle with 4 species

$$A_1 + A_2 \xrightarrow{\kappa} 2A_2,\; A_2 + A_3 \xrightarrow{\kappa} 2A_3,\; A_3 + A_4 \xrightarrow{\kappa} 2A_4, A_4 + A_1 \xrightarrow{\kappa} 2A_1$$

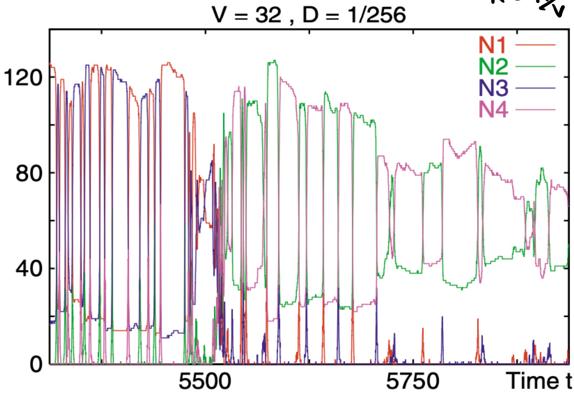
$$\emptyset \xrightarrow{\lambda} A_1 \xrightarrow{\delta} \emptyset,\; \emptyset \xrightarrow{\lambda} A_2 \xrightarrow{\delta} \emptyset,\; \emptyset \xrightarrow{\lambda} A_3 \xrightarrow{\delta} \emptyset, \emptyset \xrightarrow{\lambda} A_4 \xrightarrow{\delta} \emptyset,$$



Discreteness Induced Transitions

Togashi-Kaneko (Phys.Rev.E 2001): $V = N_{tot}(0), \kappa' = 1, D = \lambda' = \delta'$

$\kappa = \kappa'/V\ ,\ \lambda = \lambda' V\ ,\ \delta = \delta'$

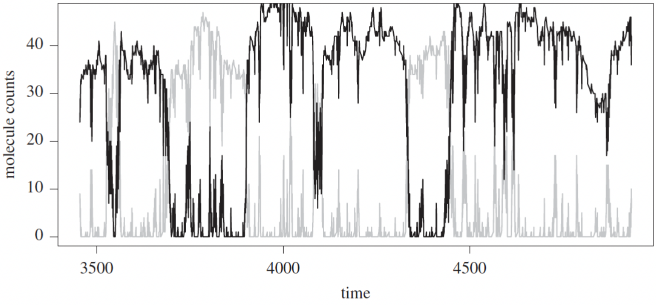


When autocatalysis is <u>faster</u> than production and degradation (and population size is smallish) dynamics <u>switches</u> between boundary states (where one or more species is absent)

Bibbona-Kim-Wiuf (J.Roy.Soc.Interface 2020): 2 species

$$A_1 + A_2 \xrightarrow{\kappa} 2A_2, \quad A_2 + A_1 \xrightarrow{\kappa} 2A_1$$

$$\emptyset \xrightarrow{\lambda} A_1 \xrightarrow{\delta} \emptyset, \ \emptyset \xrightarrow{\lambda} A_2 \xrightarrow{\delta} \emptyset$$



Bibbona-Kim-Wiuf (J.Roy.Soc.Interface 2020): Exact stationary distribution for 2-species[1]: $\pi(x_1, x_2) = \pi_y(x_1)\nu(x_1 + x_2)$ where ν is the Poisson distribution with mean $2\lambda/\delta$ and $\pi_y(\cdot)$ is the Beta-Binomial distribution with parameters $y = x_1 + x_2$, $\alpha = \beta = \delta/2\kappa$.

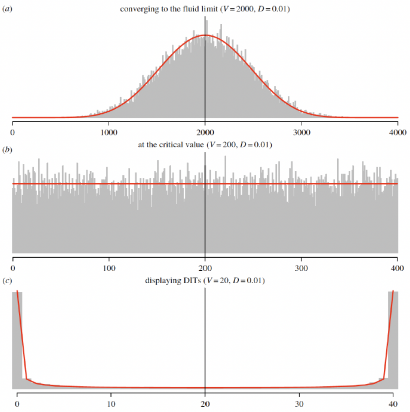


Figure: **For $\kappa' = 1, \lambda' = \delta' = 0.01$; (a) $V = 2000$, (b) $V = 200$, (c) $V = 20$.**

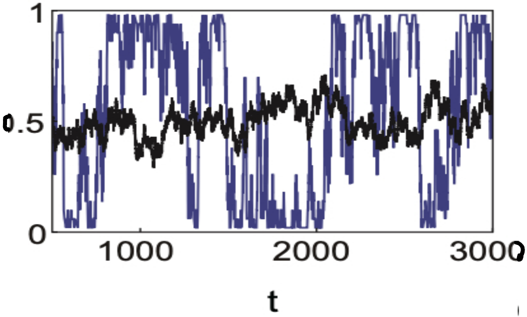
$\kappa = \frac{\kappa'}{V}$, $\lambda = \lambda' V$ (usual volume scaling)

[1] Generalizes to unequal production rates and to d species if there is autocatalysis between all pairs of species.

Saito-Kaneko (Phys.Rev.E 2015): 2 species, production & degradation replaced by mutations (slow)

$$A_1 + A_2 \xrightarrow{\kappa} 2A_2, \quad A_2 + A_1 \xrightarrow{\kappa} 2A_1$$
$$A_1 \xrightarrow{\mu_1} A_2, \; A_2 \xrightarrow{\mu_2} A_1$$

$\boldsymbol{V = N_{tot} = 50}$ **(blue)**, $\boldsymbol{N_{tot} = 2000}$ **(black)**, $\boldsymbol{\kappa' = 1, \mu_1 = \mu_2 = 0.01}$



Beyond Symmetry

• There are large population size scaling limits for autocatalytic networks with mass action kinetics → fluctuations about the stable state of an ODE.

• Most analysis for small stochastic systems assumes symmetric autocatalytic rates.

• Exception: Gallinger-Popovic (J.Roy.Soc.O.Sci. 2024) studied d species with autocatalysis between all pairs, <u>mutations</u> in place of production and degradation and <u>asymmetric</u> autocatalysis.
Asymmetry of the autocatalytic rates produced a significant asymmetry in the modes of the stationary distribution, even under very small rate differences.

Our aim: to rigorously analyse the stochastic TK model with fast <u>asymmetric</u> autocatalysis, slow production and degradation, and added mutations.

Autocatalytic reaction network

Reaction network with d species: for $i = 1, \ldots, d$ $(0 := d, d+1 := 1)$,

-autocatalytic reactions (in a cycle)

$$A_i + A_{i+1} \xrightarrow{\kappa_{i+1}} 2A_{i+1}$$

-production and degradation

$$\emptyset \xrightarrow{\lambda_i} A_i \xrightarrow{\delta_i} \emptyset$$

-mutations

$$A_i \xrightarrow{\mu_{ij}} A_j, \quad i \neq j$$

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Stochastic model: Markov chain on $\mathbb{Z}_+^d$, for $i = 1, \dots, d$,

$$X_i(t) = X_i(0) + N_i\left(\int_0^t \kappa_i X_{i-1}(s) X_i(s) ds\right) - N_{i+1}\left(\int_0^t \kappa_{i+1} X_i(s) X_{i+1}(s) ds\right)$$

$$+ N_{0i}(\lambda_i t) - N_{i0}\left(\int_0^t \delta_i X_i(s) ds\right) + \sum_{j \neq i}\left[N_{ji}\left(\int_0^t \mu_{ji} X_j(s) ds\right) - N_{ij}\left(\int_0^t \mu_{ij} X_i(s) ds\right)\right]$$

where N_i, N_{0i}, N_{i0}, $N_{ij}, j = 1, \dots, d$, $i = 1, \dots, d$ are independent Poisson processes.

Stochastic Averaging Result (FKKPRW '26)

- Separate the time scale of autocatalytic and mutation reactions from production and degradation using a separate scaling parameter $\epsilon \approx 0$ (regardless of the population size)

$$\delta_i^\varepsilon = \delta_i, \quad \lambda_i^\varepsilon = \lambda_i, \quad \kappa_i^\varepsilon = \varepsilon^{-1}\kappa_i, \quad \mu_{i,j}^\varepsilon = \varepsilon^{-1}\mu_{i,j}$$

- Mutations are dominated by autocatalytic reactions
- Stochastic averaging:

  – the total population size $Y = X_1 + \cdots + X_d$ is slow relative to the fast fluctuating $X_1, \ldots, X_d$;
  – fixing $Y = y$, individual species amounts $X_1, \ldots, X_d$ converge to a unique stationary distribution π_y;

  – the total population size converges to a birth-death process w/ birth and death rates:

$$\overline{\lambda}(y) = \lambda_1 + \cdots + \lambda_d, \quad \overline{\delta}(y) = \delta_1 E_{\pi_y}[X_1] + \cdots + \delta_d E_{\pi_y}[X_d]$$

Two Species Case (FKKPRW '26)

- Explicit expresssion for π_y: possible for $d = 2$ (by analogy with population genetics model)

$$\pi_y(x_1) \propto \kappa_1^{x_1} \kappa_2^{y-x_1} \binom{y}{x_1} \frac{(\alpha_1)_{(x_1)} (\alpha_2)_{(y-x_1)}}{(|\alpha|)_{(y)}}, \quad x_1 \in \{0, 1, \ldots, y\}$$

where

$$\alpha_1 = \frac{\mu_1}{\kappa_1}, \; \alpha_2 = \frac{\mu_2}{\kappa_2}, \; |\alpha| = \alpha_1 + \alpha_2,$$

and $(\alpha)_{(x_1)} = \alpha(\alpha+1)\ldots(\alpha+x_1-1)$ the ascending factorial

Note $\mu_1 = \mu_{21}$, $\mu_2 = \mu_{12}$

Sensitivity to asymmetry in rates

- Symmetric case - for $\kappa_1 = \kappa_2, \delta_1 = \delta_2$:

$$E_{\pi_y}[X_1] = y \frac{\alpha_1}{\alpha_1 + \alpha_2} = y \frac{\mu_1}{\mu_1 + \mu_2} \quad \text{(linear)}$$

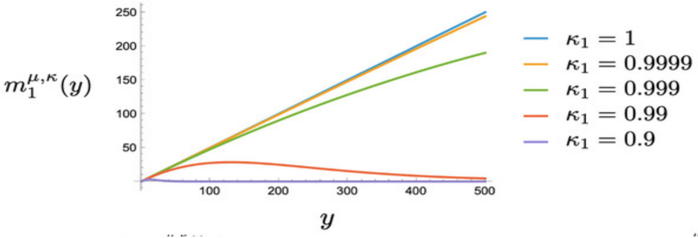
- Asymmetric case - for $\kappa_1 < \kappa_2$:
  using the Gauss hypergeometric function ${}_2F_1(-y, b, c; z)$

$$E_{\pi_y}[X_1] = y \frac{\kappa_1}{\kappa_2} \frac{\alpha_1}{\alpha_1 + \alpha_2} \frac{{}_2F_1(-y+1, \alpha_1+1, \alpha_1+\alpha_2+1; 1-\frac{\kappa_1}{\kappa_2})}{{}_2F_1(-y, \alpha_1, \alpha_1+\alpha_2; 1-\frac{\kappa_1}{\kappa_2})}$$

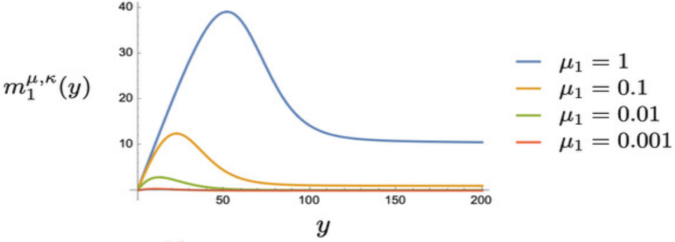
  – Asymptotics of the function ${}_2F_1(-y, b, c; z)$ for $y \to \infty$ imply

$$\lim_{y \to \infty} E_{\pi_y}[X_1] = \frac{\mu_1}{\kappa_2 - \kappa_1} \quad \text{(constant)}$$

$\kappa_2 = 1, \ \mu_1 = \mu_2 = 0.01$



$\kappa_1 = 0.9, \kappa_2 = 1, \ \mu_2 = 0.01$

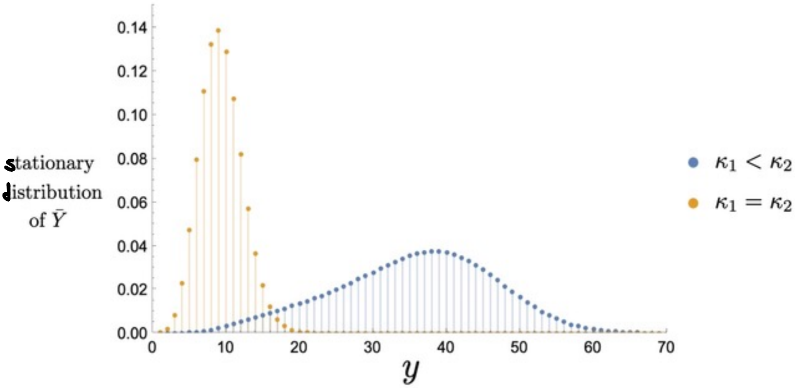


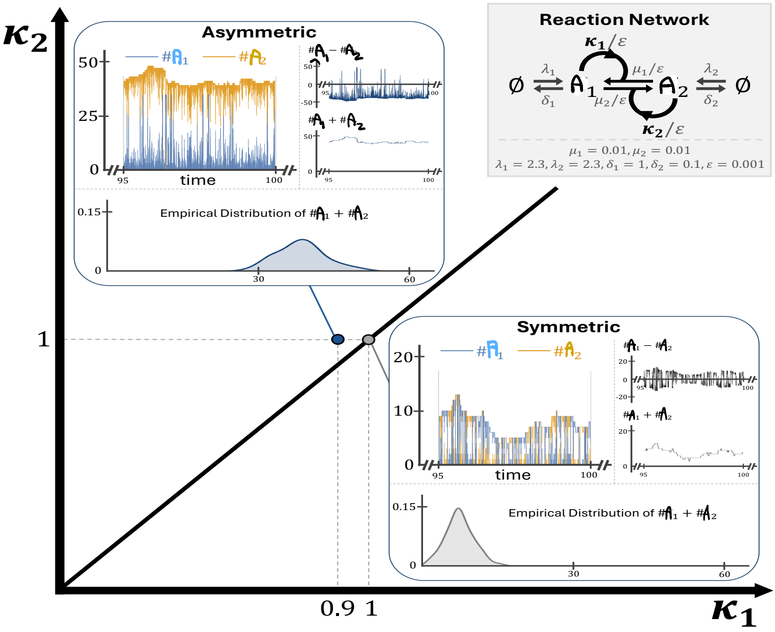
- Implications for the dynamics of the total population:
  - $\overline{Y}$ is a birth death process with

$$\overline{\lambda}(y) = \lambda_1 + \lambda_2, \;\; \overline{\delta}(y) = \delta_1 E_{\pi_y}[X_1] + \delta_2 E_{\pi_y}[X_2]$$

  - (Symmetric case): $\overline{\delta}(y) = y\frac{\delta_1\mu_1+\delta_2\mu_2}{\mu_1+\mu_2}$, and the stationary distribution of $\overline{Y}$ is Poisson with mean $\frac{(\lambda_1+\lambda_2)(\mu_1+\mu_2)}{(\delta_1\mu_1+\delta_2\mu_2)}$
  - (Asymmetric case): $\overline{\delta}(y) \sim \delta_1\frac{\mu_1}{\kappa_2-\kappa_1} + \delta_2(y - \frac{\mu_1}{\kappa_2-\kappa_1})$, and the stationary distribution of $\overline{Y}$ is no longer Poisson

$\boldsymbol{\kappa_2 = 1}$, $\boldsymbol{\mu_1 = \mu_2 = 0.01}$, $\lambda_1 = \lambda_2 = 2.3, \delta_1 = 1, \delta_2 = 0.1$





Asymmetric
#A1
#A2
50
25
0
95
time
100
#A1 − #A2
#A1 + #A2
-50
Empirical Distribution of #A1 + #A2
0.15
30
60
Reaction Network
κ_1/ε
λ_1
δ_1
μ_1/ε
μ_2/ε
λ_2
δ_2
κ_2/ε
$\emptyset \rightleftarrows A_1 \rightleftarrows A_2 \rightleftarrows \emptyset$
$\mu_1 = 0.01, \mu_2 = 0.01$
$\lambda_1 = 2.3, \lambda_2 = 2.3, \delta_1 = 1, \delta_2 = 0.1, \varepsilon = 0.001$
Symmetric
20
10
-20
κ_2
κ_1
1
0.9

Vanishing mutations

Assume $\tilde{\kappa} = \frac{\kappa_2}{\kappa_1}$ and $\tilde{\mu} = \frac{\mu_2}{\mu_1}$ are constants.

As $\mu_1 \to 0$:

$$\pi_y(x_1) = \begin{cases} \frac{\tilde{\mu}\tilde{\kappa}^{y-1}}{1+\tilde{\mu}\tilde{\kappa}^{y-1}} + O(\mu_1) & \text{for } x_1 = 0 \\ \frac{y^2}{x_1(y-x_1)} \frac{\tilde{\mu}\tilde{\kappa}^{y-x_1-1}}{1+\tilde{\mu}\tilde{\kappa}^{y-1}} \mu_1 + O(\mu_1^2) & \text{for } x_1 \in \{1, \ldots, y-1\} \\ \frac{1}{1+\tilde{\mu}\tilde{\kappa}^{y-1}} + O(\mu_1) & \text{for } x_1 = y, \end{cases}$$

Uses singular perturbation of stochastic chemical reaction networks: see Bruno, Williams, Del Vecchio (PLoS Comp. Bio. 2022), Bruno, Campos, Fu, Del Vecchio and Williams (SIAM Dyn. Systems, 2024).

Further work

- We derived a rigorous multiscale process level limit for the model, that is valid for all values of the total population size
- Sensitivity to autocatalytic rates leads to a qualitative difference with even slight asymmetry in autocatalytic rates
- Presence of this sensitivity (fragility) depends on the number of species in the network (dimension d of model): e.g. preliminary results indicate that for $d = 3$ this sensitivity is not observed, but for $d = 4$ it appears.

Abstract

Many cancer-related pathways involve molecules that promote their own production, leading to nonlinear dynamics with positive feedback loops. This mechanism underlies bistability in signaling networks where stable states can drive tumor proliferation or suppression. Stochastic fluctuations can push a system to switch between such states, so that random noise can trigger transitions from a healthy to a malignant state, or vice versa. Such systems can be modeled using stochastic autocatalytic reaction networks. Understanding the sensitivity of such stochastic systems to small parameter changes is important for the formulation of models from data, for simulation of models and for drawing conclusions for real life systems.

In this talk, we explore the sensitivity of a prototypical stochastic autocatalytic reaction network model that is known to exhibit dramatic switching behavior. The original model is called the Togashi–Kaneko model, and we consider a variant of it that allows for additional mutations. We establish a rigorous stochastic averaging principle that describes slow dynamics in terms of certain ergodic means of fast variables. For the two species model, we demonstrate a sensitivity of the model to even slight departures from symmetry in the autocatalytic reactions. We call this high sensitivity property "fragility". Our preliminary explorations for models with more than two species point to a wealth of open questions for future research. Fragility appears to be an understudied phenomenon, which is likely to affect the formulation and interpretation of autocatalytic models across a spectrum of applications in the life sciences.