LECTURE #13

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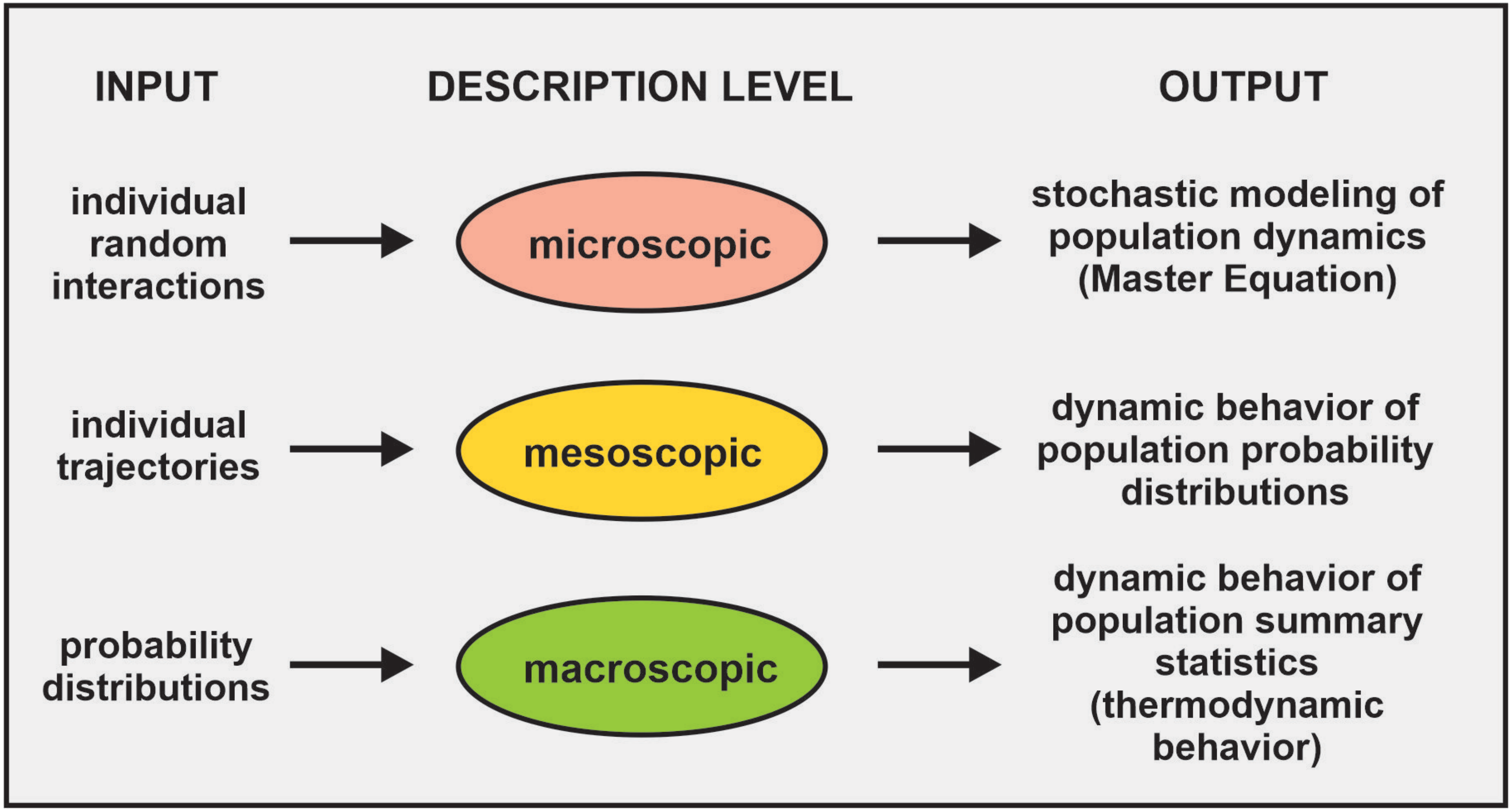
MACROSCOPIC DESCRIPTION

Description Levels of Complex Systems



Potential Energy

- To better understand what might happen at steady-state, assume that the population ME has a <u>unique</u> stationary solution

$$\bar{p}_{\mathrm{X}}(\mathbf{x};\Omega) \triangleq \lim_{t\to\infty} p_{\mathrm{X}}(\mathbf{x};t,\Omega)$$

  that is <u>independent</u> of the initial state but depends on the size parameter Ω in general.

- The probability distribution $p_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};t,\Omega)$ of the population density process $\tilde{\mathbf{X}}(t;\Omega) = \mathbf{X}(t;\Omega)/\Omega$ is given by $p_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};t,\Omega) = p_{\mathrm{X}}(\Omega\tilde{\mathbf{x}};t,\Omega)$.

Potential Energy

- Let us define the <u>potential energy function</u>:

$$V(\tilde{\mathbf{x}};\Omega) \triangleq -\frac{1}{\Omega}\ln\frac{\overline{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega)}{\overline{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}}_*;\Omega)} \geq 0$$

where

$$\overline{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega) \triangleq \lim_{t\to\infty} p_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};t,\Omega)$$

and $\tilde{\mathbf{x}}_*$ is a state at which the stationary probability distribution $\overline{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega)$ attains its <u>maximum</u> value.

- Clearly, $V(\tilde{\mathbf{x}};\Omega)$ assigns minimum (zero) potential to the states of maximum steady-state probability (which are referred to as **ground states**) and infinite potential to states of zero steady-state probability (*improbable states*).

Potential Energy

$$V(\tilde{\mathbf{x}};\Omega) \triangleq -\frac{1}{\Omega}\ln\frac{\overline{p}_{\tilde{\mathrm{x}}}(\tilde{\mathbf{x}};\Omega)}{\overline{p}_{\tilde{\mathrm{x}}}(\tilde{\mathbf{x}}_*;\Omega)} \geq 0$$

- The previous equation implies

$$\overline{p}_{\tilde{\mathrm{x}}}(\tilde{\mathbf{x}};\Omega) = \frac{1}{\zeta(\Omega)}\exp\left\{-\Omega V(\tilde{\mathbf{x}};\Omega)\right\}$$ **GIBBS DISTRIBUTION**

where

$$\zeta(\Omega) \triangleq \sum_{\mathbf{u}} \exp\left\{-\Omega V(\mathbf{u};\Omega)\right\}$$ **PARTITION FUNCTION**

Potential Energy

- Assume that, close to the thermodynamic limit, the potential energy function $V(\tilde{\mathbf{x}};\Omega)$ is an analytic function of Ω^{-1}.
- Then, a Taylor series expansion with respect to Ω^{-1} results in

$$\begin{aligned} V(\tilde{\mathbf{x}};\Omega) &= V(\tilde{\mathbf{x}};\infty) + \frac{1}{\Omega}\frac{\partial V(\tilde{\mathbf{x}};\infty)}{\partial \Omega^{-1}} + \frac{1}{\Omega^2}\frac{\partial^2 V(\tilde{\mathbf{x}};\infty)}{\partial \Omega^{-2}} + \cdots \\ &= V_0(\tilde{\mathbf{x}}) + \frac{1}{\Omega}V_1(\tilde{\mathbf{x}}) + \frac{1}{\Omega^2}V_2(\tilde{\mathbf{x}}) + \cdots \end{aligned}$$

https://en.wikipedia.org/wiki/Analytic_function

Potential Energy

$$V(\tilde{\mathbf{x}};\Omega) = V_0(\tilde{\mathbf{x}}) + \frac{1}{\Omega} V_1(\tilde{\mathbf{x}}) + \frac{1}{\Omega^2} V_2(\tilde{\mathbf{x}}) + \cdots$$

$$V_0(\tilde{\mathbf{x}}) \triangleq V(\tilde{\mathbf{x}};\infty) = -\lim_{\Omega\to\infty} \frac{1}{\Omega} \ln \frac{\overline{p}_{\tilde{\mathrm{x}}}(\tilde{\mathbf{x}})}{\overline{p}_{\tilde{\mathrm{x}}}(\tilde{\mathbf{x}}_*)} \geq 0$$

$$V_1(\tilde{\mathbf{x}}) \triangleq \frac{\partial V(\tilde{\mathbf{x}};\infty)}{\partial \Omega^{-1}}$$

$$V_2(\tilde{\mathbf{x}}) \triangleq \frac{\partial^2 V(\tilde{\mathbf{x}};\infty)}{\partial \Omega^{-2}}$$

Potential Energy and Stationary Distribution

- In this case, we approximately have that

$$\bar{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) = \frac{1}{\zeta(\Omega)} \exp\left\{-\Omega V_0(\tilde{\mathbf{x}}) - V_1(\tilde{\mathbf{x}}) - \Omega^{-1} V_2(\tilde{\mathbf{x}}) - \cdots\right\}$$

$$\zeta(\Omega) = \sum_{\mathbf{u}} \exp\left\{-\Omega V_0(\mathbf{u}) - V_1(\mathbf{u}) - \Omega^{-1} V_2(\mathbf{u}) - \cdots\right\}$$

Potential Energy and Macroscopic Behavior

- If $\chi(t)$ satisfies the macroscopic equations

$$\frac{d\chi_n(t)}{dt} = \sum_{m=1}^{M} s_{nm}\tilde{\pi}_m(\chi(t)), \quad t > 0,\ n = 1, 2, \ldots, N$$

  then, it can be shown that

$$\frac{dV_0(\chi(t))}{dt} = \sum_{n=1}^{N} \frac{\partial V_0(\chi(t))}{\partial \chi_n(t)} \frac{d\chi_n(t)}{dt} \leq 0$$

  provided that $V_0(\chi(t)) < \infty$.

- Consequently, the macroscopic solution produces dynamics that never increase the value of the potential energy function V_0.

Potential Energy and Macroscopic Behavior

- If

$$\frac{dV_0(\chi(t))}{dt} = \sum_{n=1}^{N} \frac{\partial V_0(\chi(t))}{\partial \chi_n(t)} \frac{d\chi_n(t)}{dt} < 0$$

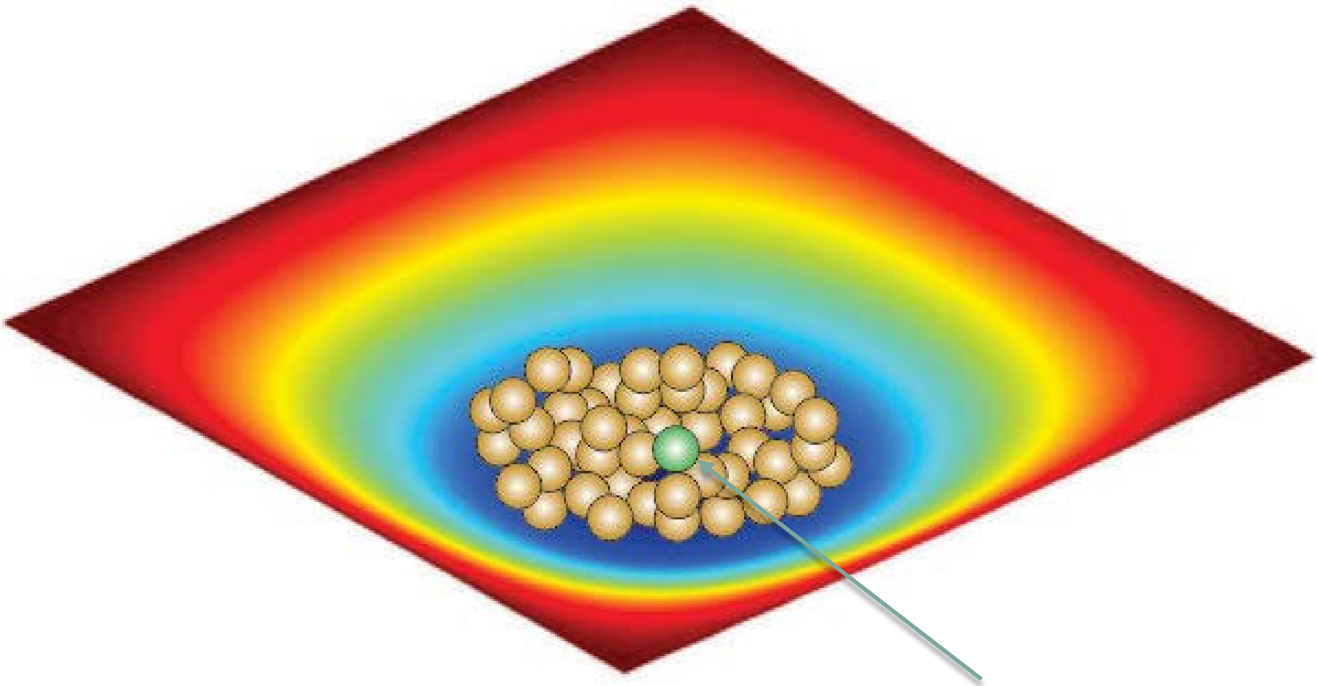
- The previous result implies that, if χ' is a <u>local minimum</u> of V_0 , then the macroscopic solution will always <u>converge</u> to χ', provided that the macroscopic system is initialized by a state that is also near χ' (this implies that χ' is an asymptotically <u>stable solution</u> of the macroscopic equations).

Potential Energy and Macroscopic Behavior

- We can view the multidimensional surface $V_0(\tilde{\mathbf{x}})$ as a potential energy landscape.
- The stable stationary states of the macroscopic equations correspond to potential wells (basins of attraction) associated with the minima of $V_0(\tilde{\mathbf{x}})$ separated by barriers, corresponding to hills associated with unstable states, and saddles associated with transitional states (states on the potential energy surface from which stable states are equally accessible).
- Which path the macroscopic system takes along the potential energy landscape will depend on the initial condition.

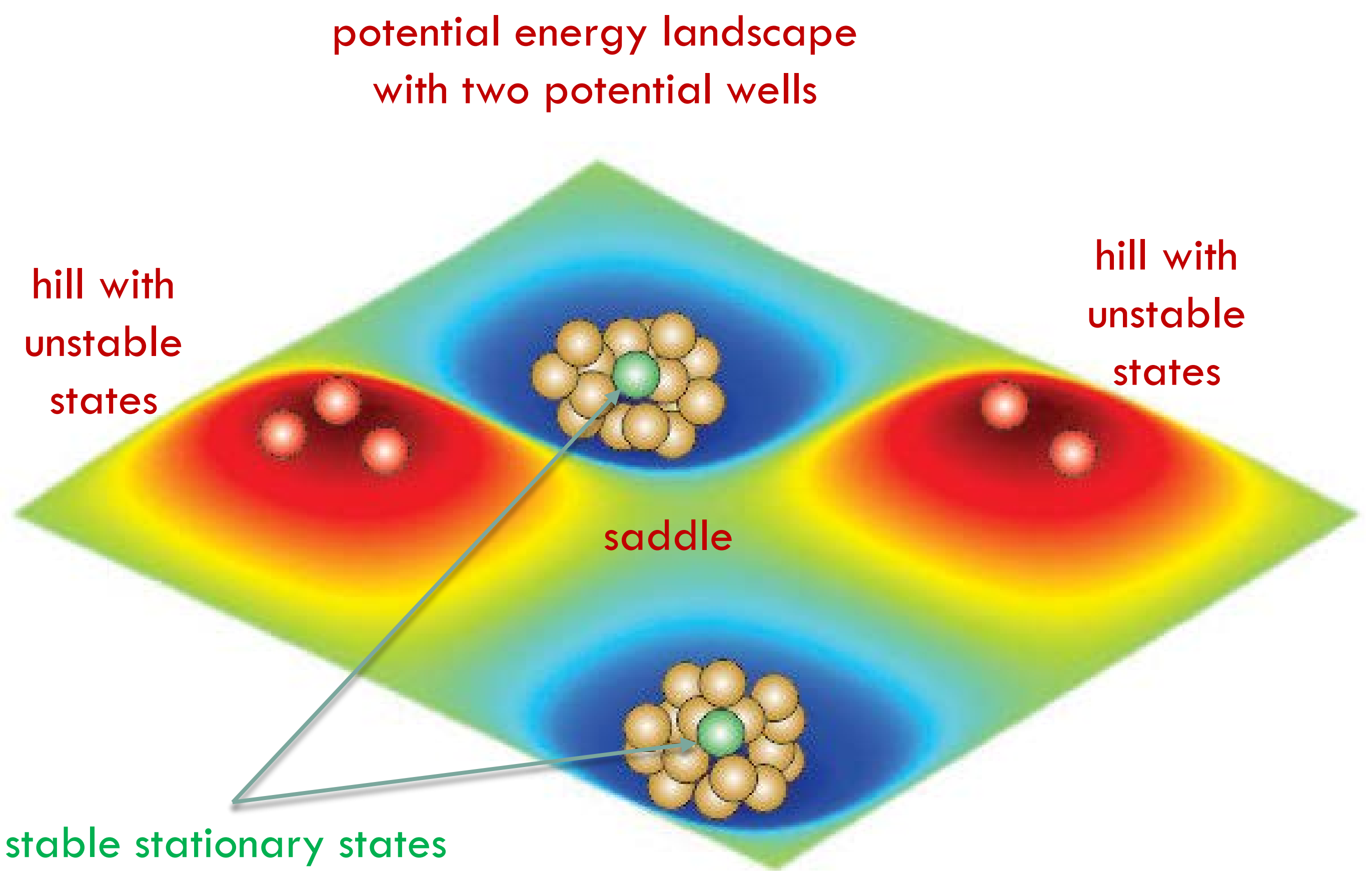
Potential Energy and Macroscopic Behavior

potential energy landscape
with one potential well



stable stationary state

Potential Energy and Macroscopic Behavior



Potential Energy and Macroscopic Behavior

- Initialization within a potential well guarantees that the macroscopic dynamics will stay within the well permanently.
- If the macroscopic system reaches a minimum of the potential energy landscape, then this minimum must be a stationary state of the macroscopic system since uphill motions are not possible since

$$\frac{dV_0(\chi(t))}{dt} \leq 0$$

If the macroscopic system reaches a minimum of the potential energy landscape, it stays there forever !!

Potential Energy and Stochastic Behavior

- For large Ω, we approximately have $V(\tilde{\mathbf{x}};\Omega) = V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}})$, in which case

$$\bar{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) = \frac{1}{\zeta(\Omega)} \exp\left\{-\Omega V_0(\tilde{\mathbf{x}}) - V_1(\tilde{\mathbf{x}})\right\}$$

$$\zeta(\Omega) = \sum_{\mathbf{u}} \exp\left\{-\Omega V_0(\mathbf{u}) - V_1(\mathbf{u})\right\}$$

- In this case, we can show that

$$\lim_{\Omega\to\infty} \bar{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) = \begin{cases} \dfrac{\exp\left\{-V_1(\tilde{\mathbf{x}})\right\}}{\sum_{\mathbf{u}\in\mathcal{G}_0} \exp\left\{-V_1(\mathbf{u})\right\}}, & \text{for } \tilde{\mathbf{x}} \in \mathcal{G}_0 \\ 0, & \text{for } \tilde{\mathbf{x}} \notin \mathcal{G}_0 \end{cases}$$

ground states of V_0

see supplement #8 for details

Potential Energy and Stochastic Behavior

$$\lim_{\Omega\to\infty} \bar{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) = \begin{cases} \dfrac{\exp\left\{-V_1(\tilde{\mathbf{x}})\right\}}{\sum_{\mathbf{u}\in\mathcal{G}_0} \exp\left\{-V_1(\mathbf{u})\right\}}, & \text{for } \tilde{\mathbf{x}} \in \mathcal{G}_0 \\ 0, & \text{for } \tilde{\mathbf{x}} \notin \mathcal{G}_0 \end{cases}$$

ground states of V_0

- In the <u>thermodynamic limit</u>, the ME asymptotically converges almost surely (with probability one) to a ground state of the potential energy function V_0, <u>independently</u> of the initial state.
- The specific ground state is chosen with probability determined by the values of the potential energy function V_1 over the ground states of V_0.
- On the other hand, the macroscopic equations might reach a minimum of V_0 <u>which may or may not be a ground state</u>, depending on the initial condition.

Keizer's Paradox

- If the macroscopic equations have a unique stable solution at steady-state that is independent of the initial condition, then V_0 will have only one (global) minimum.
- In this case, the ME will converge almost surely (with probability one) to the same state in the thermodynamic limit.
- However, if V_0 contains more than one (global or local) minimum, then the stationary solution of the ME may be different from the stationary solution predicted by the corresponding macroscopic equations.
- Consequently,

$$\boxed{\lim_{\Omega\to\infty}\lim_{t\to\infty} p_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};t,\Omega) \neq \lim_{t\to\infty}\lim_{\Omega\to\infty} p_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};t,\Omega)}$$

- This distinct difference between the stationary behavior of the ME (left-hand side of inequality) and of the macroscopic equations (right-hand side of inequality) is known as Keizer's paradox.

Potential Energy and Stochastic Behavior

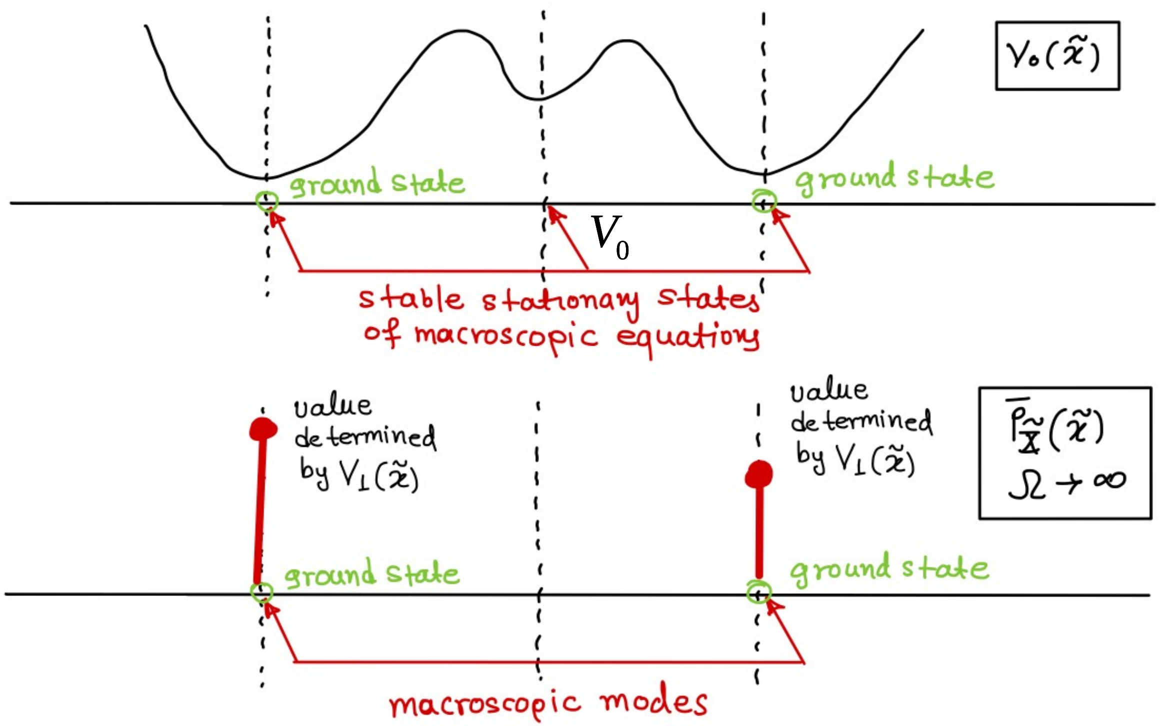
- In the thermodynamic limit as $\Omega \to \infty$, the peaks present in the stationary probability distribution $\bar{p}_{\tilde{\mathbf{X}}}(\tilde{\mathbf{x}};\infty)$ will be associated only with the global minima of V_0, which are in turn associated with stable stationary states of the macroscopic equations.

- For this reason, we refer to the peaks in $\bar{p}_{\tilde{\mathbf{X}}}(\tilde{\mathbf{x}};\infty)$ as **macroscopic modes**.

- Note however that there might be stable stationary states of the macroscopic equations that do not introduce peaks in the stationary probability distribution $\bar{p}_{\tilde{\mathbf{X}}}(\tilde{\mathbf{x}};\infty)$ and will therefore be deemed to be improbable according to the master equation approach.
- These states are associated with the local minima of V_0.

Potential Energy and Stochastic Behavior

Example:



Potential Energy and Stochastic Behavior

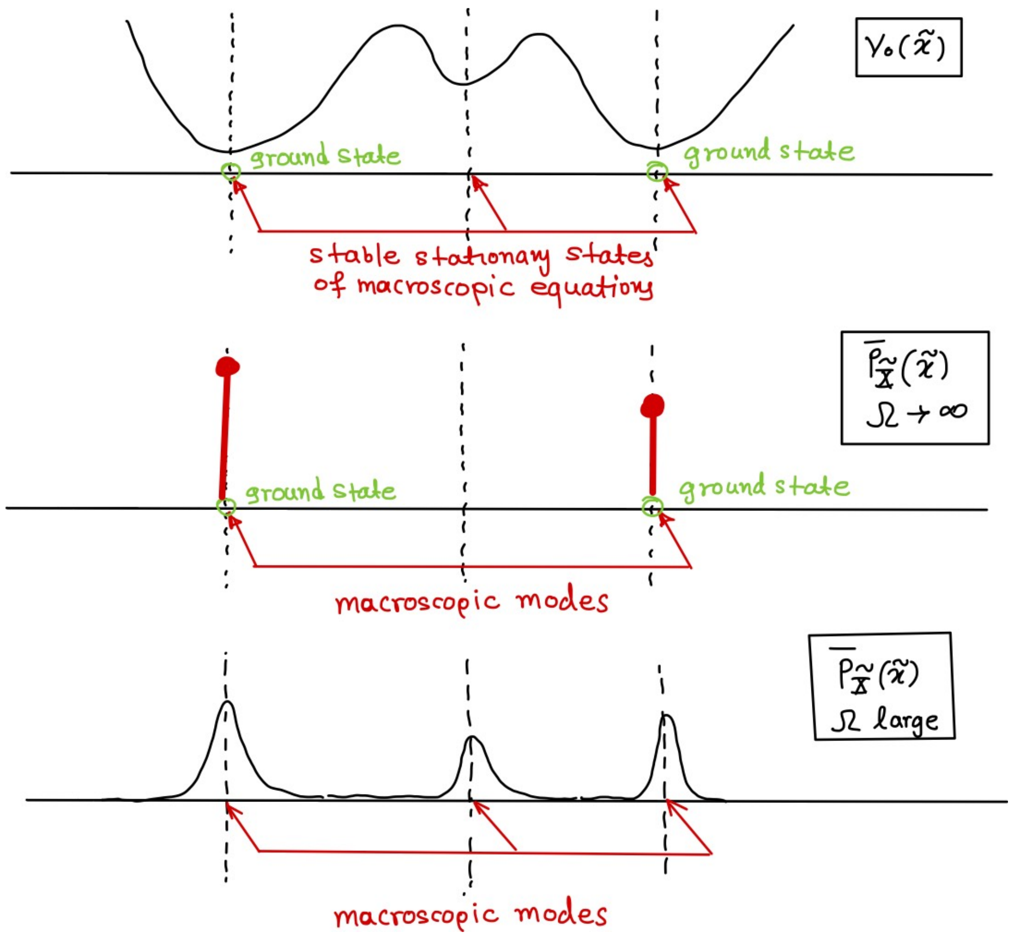
$$\overline{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) = \frac{1}{\zeta(\Omega)} \exp\left\{-\Omega V_0(\tilde{\mathbf{x}}) - V_1(\tilde{\mathbf{x}})\right\}$$

- At finite but sufficiently large sizes Ω, the <u>peaks</u> of the stationary probability distribution $\overline{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega)$ will correspond to <u>minima</u> of the potential energy landscape $V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}})$.
- In addition, and for large enough Ω, we have that $V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}}) \simeq V_0(\tilde{\mathbf{x}})$.
- We therefore expect in this case that $\tilde{\mathbf{x}}_0$ will be a minimum of $V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}})$ if and only if it is a minimum of $V_0(\tilde{\mathbf{x}})$ and the peaks of the stationary probability distribution $\overline{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega)$ will correspond to the <u>stable stationary states</u> of the macroscopic equations.

$$\begin{aligned}
\text{peaks in } \overline{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) &\Leftrightarrow \text{ min in } V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}}) \text{ [for sufficiently large but finite } \Omega] \\
&\Leftrightarrow \text{ min in } V_0(\tilde{\mathbf{x}}) \text{ [for sufficiently large but finite } \Omega] \\
&\Leftrightarrow \text{ stable macroscopic states at steady-state}
\end{aligned}$$

Potential Energy and Stochastic Behavior

- **Example:**



Potential Energy and Stochastic Behavior

- At smaller values of Ω, the stationary probability distribution will be given by

$$\bar{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega) = \frac{1}{\zeta(\Omega)} \exp\left\{ -\Omega V_0(\tilde{\mathbf{x}}) - V_1(\tilde{\mathbf{x}}) - \Omega^{-1} V_2(\tilde{\mathbf{x}}) - \cdots \right\}$$

- The modes of $\bar{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega)$ will now be determined by the minima of the potential energy landscape $V(\tilde{\mathbf{x}};\Omega) = V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}}) + \Omega^{-2} V_2(\tilde{\mathbf{x}}) + \cdots$.
- However, a state that minimizes the potential energy function V may not necessarily minimize V_0 , in which case at least some modes of the probability distribution $\bar{p}_{\tilde{\mathrm{X}}}(\tilde{\mathbf{x}};\Omega)$ will not be predicted by the corresponding macroscopic equations.

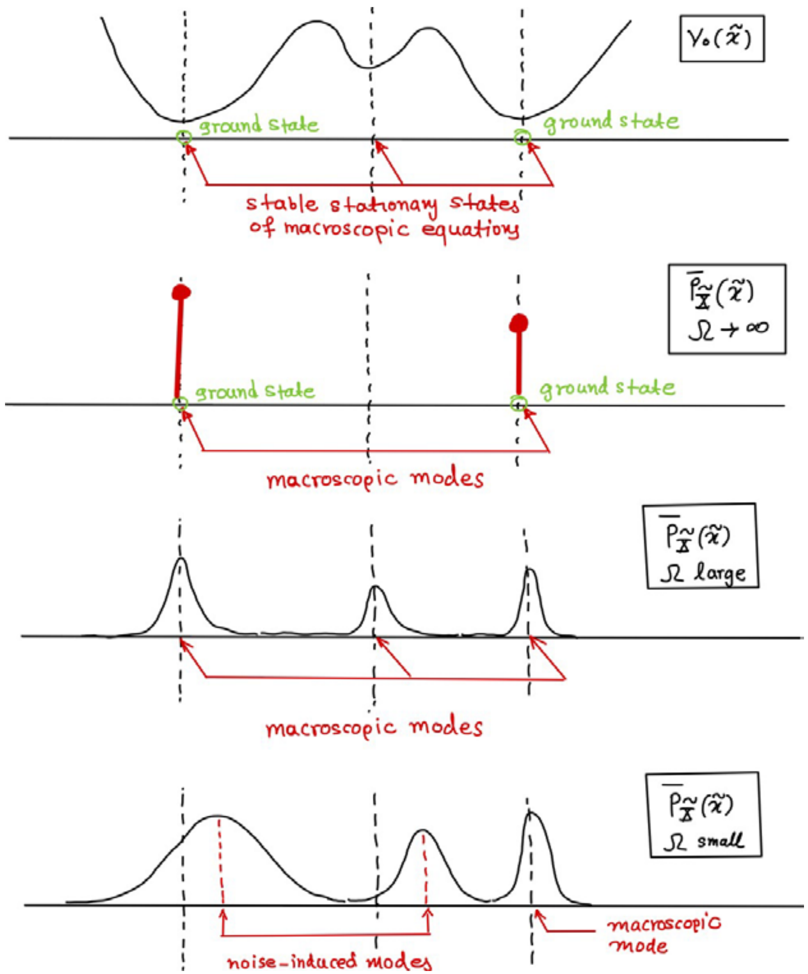
Potential Energy and Stochastic Behavior

$$\text{peaks in } \bar{p}_{\tilde{\mathbf{x}}}(\tilde{\mathbf{x}};\Omega) \Leftrightarrow \text{ min in } V(\tilde{\mathbf{x}};\Omega) = V_0(\tilde{\mathbf{x}}) + \Omega^{-1} V_1(\tilde{\mathbf{x}}) + \Omega^{-2} V_2(\tilde{\mathbf{x}}) + \cdots$$
$$\not\Leftrightarrow \text{ min of } V_0(\tilde{\mathbf{x}})$$
$$\Leftrightarrow \text{ stable macroscopic states at steady-state}$$

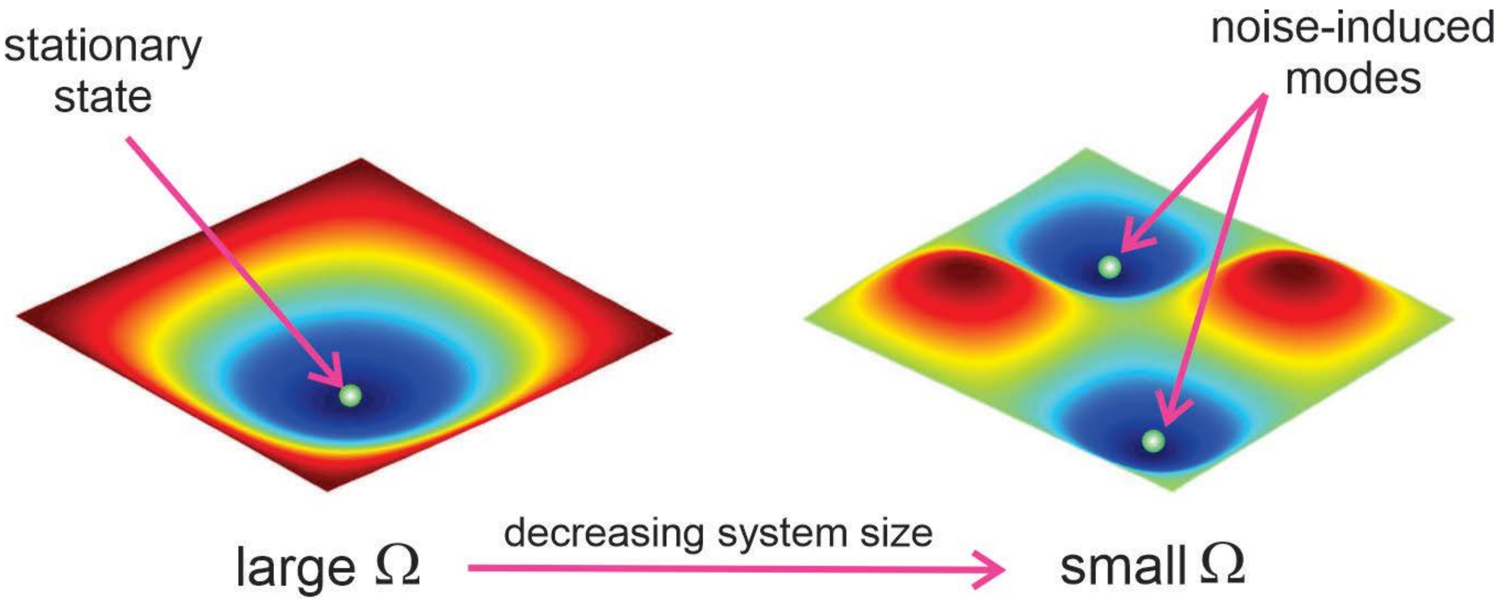
- These modes are referred to as **noise-induced modes**, since they show up at small system sizes in which appreciable stochastic fluctuations may be present in the system due to stochasticity intrinsic to the system.
- The presence of noise-induced modes in nonlinear reaction networks and their importance in modeling system behavior not accounted for by their macroscopic counterparts has been well-documented in the literature (especially in biology).

Potential Energy and Stochastic Behavior

- **Example:**

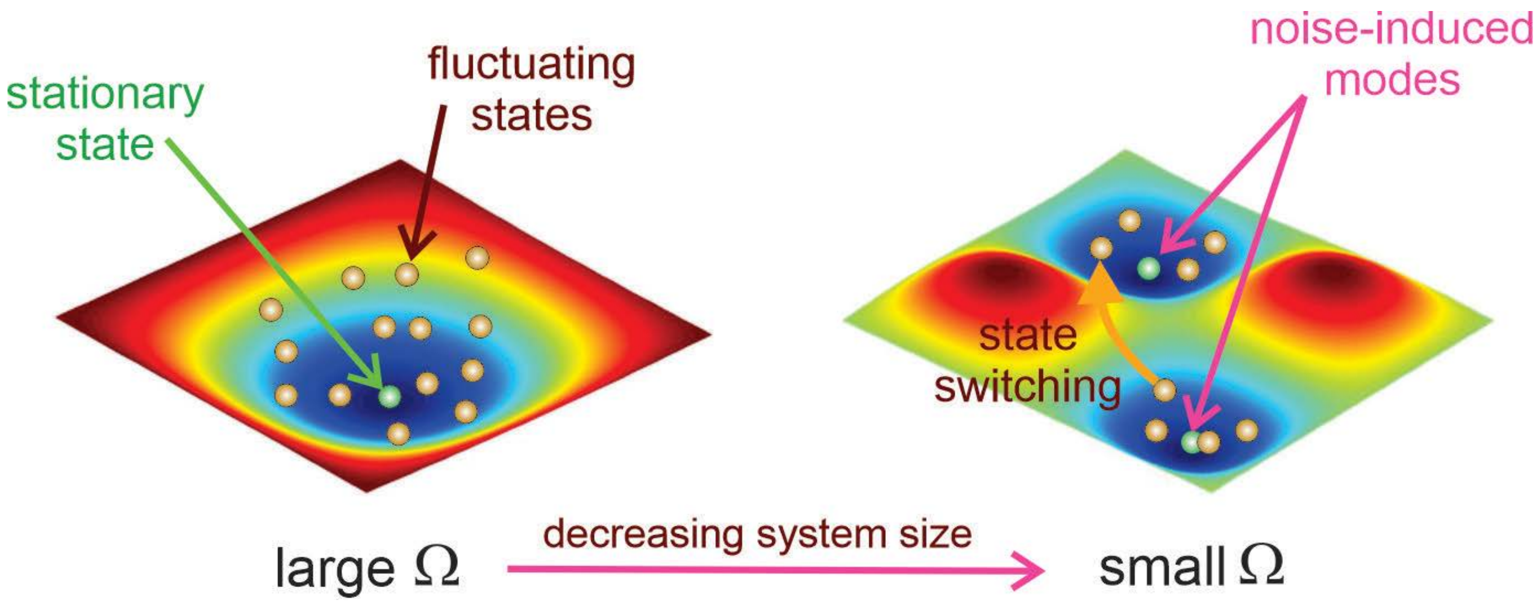


Potential Energy and Stochastic Behavior



Mode Switching

- If a Markovian reaction network is at a stable state, intrinsic stochasticity may force it to switch to another stable state at a later time.
- The probability of switching from a stable state to another stable state tends (in general exponentially) to zero as the system size increases to infinity.



Mode Switching

- At finite system sizes Ω, switching among stable stationary states becomes possible, but the probability of switching is very small for large Ω.
- Switching among stable stationary states is usually a rare event (it happens with extremely small probability).
- As a matter of fact, the waiting time for switching can be approximated by an exponential distribution with a rate parameter that tends to zero in the thermodynamic limit as $\Omega \to \infty$.
- Efficient switching between modes requires small system sizes and thus appreciable noise.