Sensitivity Analysis, Uncertainty Quantification and Inference in Stochastic Dynamics

Yannis Pantazis

University of Crete

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Sensitivity Analysis in Path-space
  Introduction
  Mathematical Theory
  Well-mixed reaction networks
  Molecular dynamics

Uncertainty Quantification and Sensitivity Bounds
  Typical observables
  Rare Events

Inference in Pathway Signalling
Joint work with

- Markos Katsoulakis (University of Massachusetts, Amherst)
- Paul Dupuis (Brown University)
- Vagelis Harmandaris (University of Crete)
- Petr Plechac (University of Delaware)
- Luc Rey-Bellet (University of Massachusetts, Amherst)
- Dion Vlachos (Chem. Engineering, University of Delaware)
- Georgios Arampatzis (Comp. Science & Engineering, ETH)
- William Hu (University of Massachusetts, Amherst)
- Tasos Tsourtis (University of Crete)
- Ioannis Tsamardinos (Comp. Science, University of Crete)
Outline

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Inference in Pathway Signalling
“Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors”, Schoeberl et al., Nature Biotechnology, 2002
Sensitivity analysis - Motivation

▶ Sensitivity Analysis: Impact in the output caused by perturbations in the input.

Perspectives on the design and control of multiscale systems, Braatz et al., 2006
Sensitivity analysis - Related concepts & Applications

- **Robustness**: The persistence of a system to a desirable state under the perturbations of external conditions.

- **Identifiability**: The ability of the experimental data and/or the model to estimate the model parameters with high fidelity.

- **Reliability**: To ensure that the performance of a system meets some pre-specified target with a given probability.

- **Optimal experimental design**: Construct experiments so that the parameters can be estimated from the resulting experimental data with the highest statistical quality. *Fisher information matrix*.

- **Uncertainty quantification**: The science of quantitative characterization and reduction of uncertainties.
Global sensitivity analysis: Study the effect of an input parameter to the output under a wide range of values or under a specified distribution.

Local sensitivity analysis: Fix input parameters to a value and study the effect of small perturbations around the fixed parameter to the output. Local SA is typically a prerequisite for global SA.

Observable-based SA. Let $\{x_t\}$ is a stochastic process depending on $\theta \in \mathbb{R}$ and $f$ is an observable. Compute

$$S_{P_\theta,t}, f(\theta) = \frac{d}{d\theta} \mathbb{E}_{P_\theta}[f(x)]$$

Density-based SA. Compare unperturbed and perturbed densities utilizing a metric or a divergence or compute the Fisher information matrix.
Sensitivity analysis - Challenges

- Perform SA on **stochastic** systems.
- Perform SA for computational models with a **very large number of parameters**.
- Tackling with **non-equilibrium** and/or **out-of-equilibrium** stochastic systems.
- Infer sensitivity information about the **dynamics** of a stochastic process.
- Perform SA **fast and reliable**.
  - **Reduction of variance** of statistical estimators.
Let \( \{x_m\}_{m \in \mathbb{Z}_+} \) be a discrete-time Markov chain at steady states.

The path distribution from 0 to \( T \) is given by

\[
Q_{0,T}^\theta (x_0, \ldots, x_T) = \mu^\theta (x_0) p^\theta (x_0, x_1) \cdots p^\theta (x_{T-1}, x_T)
\]

where

- \( \theta \in \mathbb{R}^K \) is the parameter vector.
- \( \mu^\theta (x) \) is the stationary distribution.
- \( p^\theta (x, x') \) is the transition probability function.
Suggest performing parameter sensitivity analysis by comparing the path distributions utilizing relative entropy.

**Definition:** The path relative entropy of $Q_{0,T}^\theta$ w.r.t. $Q_{0,T}^{\theta+\epsilon}$ is

$$\mathcal{R} \left( Q_{0,T}^\theta \| Q_{0,T}^{\theta+\epsilon} \right) := \int \log \left( \frac{dQ_{0,T}^\theta}{dQ_{0,T}^{\theta+\epsilon}} \right) dQ_{0,T}^\theta$$

**Properties:**

- (i) $\mathcal{R} \left( Q_{0,T}^\theta \| Q_{0,T}^{\theta+\epsilon} \right) \geq 0$ and
- (ii) $\mathcal{R} \left( Q_{0,T}^\theta \| Q_{0,T}^{\theta+\epsilon} \right) = 0$ iff $Q_{0,T}^\theta = Q_{0,T}^{\theta+\epsilon}$
- (iii) $\mathcal{R} \left( Q_{0,T}^\theta \| Q_{0,T}^{\theta+\epsilon} \right) \leq \mathcal{R} \left( Q_{0,T+1}^\theta \| Q_{0,T+1}^{\theta+\epsilon} \right)$
The relative entropy rate (RER) is defined as

\[ H(Q^\theta \| Q^{\theta+\epsilon}) = \lim_{T \to \infty} \frac{1}{T} \mathcal{R}(Q_{0,T}^\theta \| Q_{0,T}^{\theta+\epsilon}) \]

Easy to show that

\[ H(Q^\theta \| Q^{\theta+\epsilon}) = \mathbb{E}_{\mu^\theta} \left[ \int p^\theta(x, x') \log \frac{p^\theta(x, x')}{p^{\theta+\epsilon}(x, x')} d x' \right] \]
The relative entropy rate (RER) is defined as

\[ \mathcal{H}(Q^\theta \| Q^{\theta+\epsilon}) = \lim_{T \to \infty} \frac{1}{T} \mathcal{R}\left(Q^0_{0,T} \| Q^{\theta+\epsilon}_{0,T}\right) \]

Easy to show that

\[ \mathcal{H}(Q^\theta \| Q^{\theta+\epsilon}) = \mathbb{E}_{\mu^\theta} \left[ \int p^\theta(x, x') \log \frac{p^\theta(x, x')}{p^{\theta+\epsilon}(x, x')} \, dx' \right] \]

Under smoothness assumption on $\theta$, it holds that

\[ \mathcal{H}(Q^\theta \| Q^{\theta+\epsilon}) = \frac{1}{2} \epsilon^T \mathcal{I}_\mathcal{H}(Q^\theta) \epsilon + O(|\epsilon|^3) \]

where path Fisher information matrix is defined as

\[ \mathcal{I}_\mathcal{H}(Q^\theta) = \mathbb{E}_{\mu^\theta} \left[ \int p^\theta(x, x') \nabla_{\theta} \log p^\theta(x, x') \nabla_{\theta} \log p^\theta(x, x')^T \, dx' \right] \]
What do we gain?

- **RER** contains information not only for the invariant measure but also for the stationary dynamics such as metastable dynamics, time correlations, etc..
- No need for explicit knowledge of invariant measure.
- **RER** is an observable of known test function $\Rightarrow$ tractable and statistical estimators can provide easily and efficiently its value.
- Different $\epsilon$’s $\Rightarrow$ SA at different directions.

- **FIM** constitutes a derivative-free sensitivity analysis method.
- Robustness on parameter perturbations as well as parameter identifiability can be inferred from the **FIM**.
  - Wider **FIM** implies a more robust model.
  - Steeper **FIM** implies more identifiable parameters.
Well-mixed reaction networks

- A continuous-time jump Markov process is fully determined by the transition rates, \( c(x, x') \).
  - The total rate is defined by \( \lambda(x) = \sum_{x'} c(x, x') \).
- Relative entropy rate:
  \[
  \mathcal{H} (Q^\theta \parallel Q^{\theta+\epsilon}) = \mathbb{E}_{\mu^\theta} \left[ \sum_{x'} c^\theta(x, x') \log \frac{c^\theta(x, x')}{c^{\theta+\epsilon}(x, x')} - (\lambda^\theta(x) - \lambda^{\theta+\epsilon}(x)) \right]
  \]
  - Derived using Girsanov formula for \( dQ^\theta_{0,T}/dQ^{\theta+\epsilon}_{0,T} \).
- Path Fisher information matrix:
  \[
  I(H)(Q^\theta) := \mathbb{E}_{\mu^\theta} \left[ \sum_{x'} c^\theta(x, x') \nabla_\theta \log c^\theta(x, x') \nabla_\theta \log c^\theta(x, x')^T \right]
  \]
Path FIM - Epidermal Growth Factor Receptor

Left panel: The graph representation of the dependencies between the reactions (left column) and the model parameters (right column). Right panel: The corresponding block-diagonal structure of the FIM.

Diagonal elements of the path FIM computed at the steady state regime (upper) and at the transient regime (lower) for EGFR. Parameter sensitivities differ by orders of magnitude; known as “sloppiness” in biology.
Info-theoretic Sensitivity Analysis in Path-space (ISAP)

- ISAP: performs simulation and sensitivity analysis for reaction networks.
- http://people.math.umass.edu/~pantazis/source/ISAP.zip
A system of stochastic differential equations with $N$ particles:

\[
\begin{aligned}
dq_t &= M^{-1} p_t dt \\
dp_t &= F^\theta(q_t) dt - \gamma M^{-1} p_t dt + \sigma dW_t,
\end{aligned}
\]

Relative entropy rate:

\[
\mathcal{H}(Q^\theta \| Q^{\theta+\epsilon}) = \frac{1}{2} \mathbb{E}_{\mu^\theta} [ (F^{\theta+\epsilon}(q) - F^\theta(q))^T (\sigma \sigma^T)^{-1} (F^{\theta+\epsilon}(q) - F^\theta(q)) ]
\]

Path Fisher information matrix:

\[
\mathcal{I}_{\mathcal{H}}(Q^\theta) = \mathbb{E}_{\mu^\theta} [ \nabla_\theta F^\theta(q)^T (\sigma \sigma^T)^{-1} \nabla_\theta F^\theta(q) ]
\]

“Sensitivity Analysis for Stochastic Molecular Systems using Information Metrics”, A. Tsourtis, Y.P., M. Katsoulakis and V. Harmandaris, JCP.

Methane - $\text{CH}_4$
Per particle RER and FIM-approximated RER comparison with 5% perturbation in all the parameters. The parameters are grouped according to their order of magnitude.

- Relative Entropy Rate (RER) estimator
- FIM-based RER estimator

### Parameters and Results
- \( C-C \)
- \( C-H \)
- \( H-H \)
- \( K_r \)
- \( K_\theta \)
- \( r_0 \)
- \( \theta_0 \)
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Connection with observable-based SA

Question: Are there any links between density-based approaches (relative entropy, FIM) and observable-based approaches ($S_{P_{\theta},f}(\theta) = \partial_{\theta} \mathbb{E}_{P_{\theta}}[f]$)?
Connection with observable-based SA

▶ **Question:** Are there any links between density-based approaches (relative entropy, FIM) and observable-based approaches ($S_{P\theta,f}(\theta) = \partial_\theta \mathbb{E}_{P\theta}[f]$)?
▶ Based on Pinsker (or Csiszar-Kullback-Pinsker) inequality:

$$|\mathbb{E}_Q[f] - \mathbb{E}_P[f]| \leq ||f||_\infty \sqrt{2\mathcal{R}(Q\|P)}$$

▶ $Q$: “true” probabilistic model
▶ $P$: “nominal” or “reference” model
Connection with observable-based SA

- **Question**: Are there any links between density-based approaches (relative entropy, FIM) and observable-based approaches ($S_{P_\theta,f}(\theta) = \partial_\theta \mathbb{E}_{P_\theta}[f]$)?
- Based on Pinsker (or Csiszar-Kullback-Pinsker) inequality:

  $$|\mathbb{E}_Q[f] - \mathbb{E}_P[f]| \leq ||f||_\infty \sqrt{2R(Q \| P)}$$

- $Q$: “true” probabilistic model
- $P$: “nominal” or “reference” model

- For any bounded $f$ with finite $\Lambda(c)$ around 0, **UQ information inequalities** (Chowdhary & Dupuis, ESAIM ’13, Li & Xiu, ’12, SIAM Sci. Comp.):

  $$\sup_{c > 0} -\frac{\Lambda(-c) + R(Q \| P)}{c} \leq \mathbb{E}_Q[f] - \mathbb{E}_P[f] \leq \inf_{c > 0} \frac{\Lambda(c) + R(Q \| P)}{c}$$

- $\Lambda(c) := \log \mathbb{E}_P[\exp\{c(f - \mathbb{E}_P[f])\}]$: cumulant generating function.
- Based on the Donsker-Varadhan variational formula for relative entropy.
Uncertainty Quantification Bounds

- **Theorem**: Define

\[ \Xi^+_\left( Q \parallel P ; f \right) := \inf_{c > 0} \frac{\Lambda(c) + R \left( Q \parallel P \right)}{c} \]

Then, \( \Xi^+_\left( Q \parallel P ; f \right) \) is a goal-oriented divergence that couples the observable \( f \) and the relative entropy.

- That means
  (i) \( \Xi^+_\left( Q \parallel P ; f \right) \geq 0 \)
  (ii) \( \Xi^+_\left( Q \parallel P ; f \right) = 0 \) iff \( Q = P \) or \( f = \mathbb{E}[f] \) \( P \)-a.s.
**Theorem**: Explicit representations of $\Xi_+$:

$$
\Xi_+(Q \parallel P; f) = \tilde{\Lambda}^{-1}(\mathcal{R}(Q \parallel P)) \\
= \Lambda'(\Phi^{-1}(\mathcal{R}(Q \parallel P))) \\
= \sqrt{2 \text{Var}_P(f)} \sqrt{\mathcal{R}(Q \parallel P)} + O(\mathcal{R}(Q \parallel P))
$$

- $\tilde{\Lambda}(k) = \sup_{c>0}\{ck - \tilde{\Lambda}(c)\}$: Legendre transform of $\Lambda(\cdot)$.
- $\Phi(c) := \Lambda(c) + c\Lambda'(c)$ is related with the Legendre transform of $\Lambda(\cdot)$.
- Relative entropy controls the uncertainty.
Sensitivity Bounds

- **Sensitivity bound** for observable $f$:

  \[ |S_{\mu^\theta,f}(\theta)| \leq \sqrt{\text{Var}_{\mu^\theta}(f)} \sqrt{\mathcal{I}(\mu^\theta)} \]

  - Obtained by setting $Q = \mu^{\theta+\epsilon}$, $P = \mu^\theta$, divide by $\epsilon$ and send $\epsilon \to 0$.
  - Related to the generalized Cramer-Rao theorem (Estimation theory).
  - **Intergovernmental panel for climate change** uses as sensitivity index:

    \[ \frac{|S_{\mu^\theta,f}(\theta)|}{\text{Std}_{\mu^\theta}(f)} \leq \sqrt{\mathcal{I}(\mu^\theta)} \]

  - But, in non-equilibrium systems, $\mu^\theta$ is usually **not** known.
Sensitivity Bounds

- Sensitivity bound for time-averaged observable
  \[ F(x) = \frac{1}{T} \int_0^T f(x_t) dt : \]
  \[ |S_{Q^\theta, F(\theta)}| \leq \sqrt{\tau_{\mu^\theta}(f)} \sqrt{\mathcal{I}_H(Q^\theta)} \]

- \[ \tau_{\mu^\theta}(f) := \int_\infty^{-\infty} < f(x_t), f(x_0) >_{\mu^\theta} dt \] is the integrated autocorrelation time.
- More general theory for transient, long-time, infinite time and spatially-extended regimes.
Another biological model that describes Epidermal Growth Factor Receptor. [Kholodenko et.al., J. Biol. Chem., 1999]

23 species, 47 reactions, 50 parameters, $23 \times 50 = 1150$ sensitivity indices ($S_{ij} = \partial_{\theta_j} \mathbb{E}[X_i]$).
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Sensitivity analysis for rare events

- An event $A$ is rare if $P(A) = \mathbb{E}_P[\chi_A] \ll 1$. We usually consider $\log P(A)$.
  - Applications to: Reliability analysis, queuing theory, operations research, insurance, statistical mechanics.

- Sensitivity analysis for rare events:

  \[
  S_A(P^\theta) := \partial_\theta \log P^\theta(A) = \frac{\partial_\theta P^\theta(A)}{P^\theta(A)}
  \]

  - Extremely few previous studies on this area!
  - Relative entropy is not the most appropriate divergence.
Sensitivity analysis for rare events

- An event $A$ is **rare** if $P(A) = \mathbb{E}_P[\chi_A] \ll 1$. We usually consider $\log P(A)$.
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- Sensitivity analysis for **rare events**:

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  - Extremely few previous studies on this area!
  - Relative entropy is not the most appropriate divergence.

- **Rare event bounds** based on **Renyi divergence** (*Atar, Chowdhary and Dupuis, SIAM UQ ’14*):

  $$\frac{1}{\alpha - 1} \log Q(A) - \frac{1}{\alpha} \mathcal{R}_\alpha (Q \parallel P) \leq \frac{1}{\alpha} \log P(A) \leq \frac{1}{\alpha + 1} \log Q(A) + \frac{1}{\alpha + 1} \mathcal{R}_{\alpha + 1} (P \parallel Q)$$

- **Renyi divergence**: 

  $$\mathcal{R}_\alpha (Q \parallel P) := \frac{1}{\alpha - 1} \log \mathbb{E}_P \left[ \left( \frac{dQ}{dP} \right)^\alpha \right] = \frac{1}{\alpha - 1} \log \mathbb{E}_P \left[ e^{\alpha \log \frac{dQ}{dP}} \right]$$


Sensitivity analysis for rare events

- **UQ bound:**
  \[
  \sup_{\alpha > 0} \frac{H(-\alpha) - \log P(A)}{\alpha} \leq \log Q(A) - \log P(A) \leq \inf_{\alpha > 0} \frac{H(\alpha) - \log P(A)}{\alpha}
  \]

- \( H(\alpha) := \log \mathbb{E}_P[\exp\{\alpha \log \frac{dQ}{dP}\}] \): cumulant generating function of \( \log \frac{dP}{dQ} \).
Sensitivity analysis for rare events

- **UQ bound:**
  \[
  \sup_{\alpha > 0} - \frac{H(-\alpha) - \log P(A)}{\alpha} \leq \log Q(A) - \log P(A) \leq \inf_{\alpha > 0} \frac{H(\alpha) - \log P(A)}{\alpha}
  \]

- \(H(\alpha) := \log \mathbb{E}_P[\exp\{\alpha \log \frac{dQ}{dP}\}]:\) cumulant generating function of \(\log \frac{dP}{dQ}\).

- Does these bounds remind you something?
Sensitivity analysis for rare events

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  \[ \sup_{\alpha > 0} - \frac{H(-\alpha) - \log P(A)}{\alpha} \leq \log Q(A) - \log P(A) \leq \inf_{\alpha > 0} \frac{H(\alpha) - \log P(A)}{\alpha} \]

- **\( H(\alpha) := \log \mathbb{E}_P[\exp\{\alpha \log \frac{dQ}{dP}\}] \): cumulant generating function of \( \log \frac{dP}{dQ} \).**

- **Does these bounds remind you something?**
  \[ \sup_{c > 0} - \frac{\Lambda(-c) + \mathcal{R}(Q \| P)}{c} \leq \mathbb{E}_Q[f] - \mathbb{E}_P[f] \leq \inf_{c > 0} \frac{\Lambda(c) + \mathcal{R}(Q \| P)}{c} \]
Sensitivity analysis for rare events

- **Sensitivity bounds** \((Q = P^\theta + \epsilon, \ P = P^\theta \) and \(\alpha = \frac{1}{\epsilon}(\alpha_0 + O(\epsilon)))\):

\[
\sup_{\alpha > 0} -\frac{\bar{H}(-\alpha) - \log P^\theta(A)}{\alpha} \leq S_A(P^\theta) \leq \inf_{\alpha > 0} \frac{\bar{H}(\alpha) - \log P^\theta(A)}{\alpha}
\]

- \(\bar{H}(\alpha) := \log \mathbb{E}_P[\exp\{\alpha \partial_\theta \log P^\theta\}]\): cumulant generating function of \(\partial_\theta \log P^\theta\).
Sensitivity analysis for rare events

- Sensitivity bounds \((Q = P^\theta + \epsilon, \ P = P^\theta \text{ and } \alpha = \frac{1}{\epsilon}(\alpha_0 + O(\epsilon)))\):

\[
\sup_{\alpha > 0} - \frac{\tilde{H}(-\alpha) - \log P^\theta(A)}{\alpha} \leq S_A(P^\theta) \leq \inf_{\alpha > 0} \frac{\tilde{H}(\alpha) - \log P^\theta(A)}{\alpha}
\]

- \(\tilde{H}(\alpha) := \log \mathbb{E}_P[\exp\{\alpha \partial_\theta \log P^\theta\}]\): cumulant generating function of \(\partial_\theta \log P^\theta\).

- Extensions to bound rate function derivatives (Large Deviations, Moderate Deviations, etc).

- “Sensitivity Bounds for Rare Events based on Renyi Divergence”, P. Dupuis, M. Katsoulakis, Y.P. and L. Rey-Bellet
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Mass cytometry

- CYTOF: Single-cell measurements
- Nolan group at Stanford, 2010-2012
- Can measure 40-60 proteins simultaneously compared to 3-8 of flow cytometry
Mass cytometry - Data

“Multiplexed mass cytometry profiling of cellular states perturbed by small-molecule regulators”, Bodenmiller et al., Nature Biotechnology, 2012
Dynamical model

- System of ODEs:

\[ \dot{x} = A\psi(x) + u, \quad x(0) = x_0 \]

- \( x = x(t) \in \mathbb{R}^N \): State (or variable) vector
- \( A \in \mathbb{R}^{N \times Q} \): Parameter matrix
- \( \psi : \mathbb{R}^N \to \mathbb{R}^Q \): Vector-valued vector function
- \( u = u(t) : \mathbb{R} \to \mathbb{R}^N \): Intervention vector function

- **Goal:** Given measurements and \( \psi(\cdot) \) estimate \( A \).
  - Structure estimation \( \iff \) finding the zeros of matrix \( A \).
  - Parameter estimation \( \iff \) estimate the non-zero elements of \( A \).
Ingredients:

- Handle **sparse sampling** using Collocation method (ie, time-series interpolation).
- Handle **multiple interventions** using Multiple shooting.
- Add ODE equations as **soft constraints**.
- Deal with **sparsity** of $A$ using **LASSO**-type cost functional.
  - LASSO: Least Absolute Shrinkage and Selection Operator
  - $\lambda_A$: weight that controls the sparsity.
- Overall optimize a **nonlinear** cost functional.
### ABCDEFG - An example

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Propensity</th>
<th>Rate constant ((k_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A \to B)</td>
<td>(k_1x_A)</td>
<td>0.01</td>
</tr>
<tr>
<td>(B \to C)</td>
<td>(k_2x_B)</td>
<td>0.04</td>
</tr>
<tr>
<td>(B \to D)</td>
<td>(k_3x_B)</td>
<td>0.1</td>
</tr>
<tr>
<td>(C \to E)</td>
<td>(k_4x_C)</td>
<td>0.1</td>
</tr>
<tr>
<td>(C \to F)</td>
<td>(k_5x_C)</td>
<td>0.01</td>
</tr>
<tr>
<td>(D \to C)</td>
<td>(k_6x_D)</td>
<td>0.2</td>
</tr>
<tr>
<td>(E \to D)</td>
<td>(k_7x_E)</td>
<td>0.4</td>
</tr>
<tr>
<td>(E \to G)</td>
<td>(k_8x_E)</td>
<td>0.01</td>
</tr>
<tr>
<td>(F \to G)</td>
<td>(k_9x_F)</td>
<td>0.01</td>
</tr>
<tr>
<td>(G \to A)</td>
<td>(k_{10}x_G)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

- Matrix A has 17 nonzero elements out of 49.
ABCDEFG - Error

![Graph showing sensitivity analysis in path-space with uncertainty quantification and sensitivity bounds, including inference in pathway signalling.](image)

- **Outline**:
  - Sensitivity Analysis in Path-space
  - Uncertainty Quantification and Sensitivity Bounds
  - Inference in Pathway Signalling

- **Equation**:

\[
\log_{10}(\lambda_A)
\]

- **Graph Details**:
  - Three graphs show the relationship between RXOR and \(\log_{10}(\lambda_A)\) for different values of \(R\) and SNR.
  - The graphs illustrate how changes in \(R\) and SNR affect the sensitivity analysis.

- **Authors**:
  - Yannis Pantazis
  - University of Crete

- **Title**:

SA, UQ and Inference for Stochastic Dynamics
References


6. ISAP-MATLAB package for sensitivity analysis of high-dimensional stochastic chemical networks, W. Hu - M. Katsoulakis - Y.P. (submitted)


The end

THANK YOU!!!