MATH:7450 (22M:305) Topics in Topology: Scientific and Engineering Applications of Algebraic Topology

Dec 6, 2013: An elementary introduction to modeling regulatory networks.

Fall 2013 course offered through the University of Iowa Division of Continuing Education

Isabel K. Darcy, Department of Mathematics Applied Mathematical and Computational Sciences, University of Iowa

http://www.math.uiowa.edu/~idarcy/AppliedTopology.html
Detecting Morse Decompositions of the Global Attractor of Regulatory Networks by Time Series Data

Hiroshi Kokubu (Kyoto University)

Journal of Theoretical Biology 335 (2013) 130–146

Dynamics and control at feedback vertex sets. II: A faithful monitor to determine the diversity of molecular activities in regulatory networks*

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Example of a regulatory network
\[
\frac{d(gene_1)}{dt} = k_{1,s} \cdot \frac{1}{1 + k_{1,3} \cdot gene_3} - k_{1,d} \cdot gene_1
\]

\[
\frac{d(gene_2)}{dt} = k_{2,s} \cdot \frac{k_{2,1} \cdot gene_1}{1 + k_{2,1} \cdot gene_1} - k_{2,d} \cdot gene_2
\]

\[
\frac{d(gene_3)}{dt} = k_{3,s} \cdot \frac{k_{3,1} \cdot gene_1 \cdot k_{3,2} \cdot gene_2}{(1 + k_{3,1} \cdot gene_1) \cdot (1 + k_{3,2} \cdot gene_2)} - k_{3,d} \cdot gene_3
\]
Angiogenic signaling network.

Abdollahi A et al. PNAS 2007;104:12890-12895
The diagram illustrates the process of transitioning between states A and B. The 3D graphs on the left show the function $f_A$ and $f_B$ as functions of $x_A$ and $x_B$. The graph on the right represents the dynamics in the $x_A$ and $x_B$ plane, indicating the flow of states from A to B and back.
\[ x' = -4x - y \]
\[ y' = -3x + 2y \]
Classification of steady states of a 2-D linear system.

- Centre: $\text{tr } J = 0$
- Stable node
- Unstable node
- Stable spiral
- Unstable spiral
- Saddle Point

$\text{tr } J = (\det J)/4$

[Diagram showing various types of phase portraits and their classification based on the eigenvalues of the Jacobian matrix.]
Difficulties

• Difficult to observe the dynamics of the activity of bio-molecules with sufficient time resolution. Most data obtained = snapshots.

• Regulatory networks are possibly incomplete. We can never exclude the possibility that unknown species of molecules or unknown regulations may have an important role.

• Information on the regulatory network alone is not sufficient to determine the resulting dynamics. Numerical simulations rely on many unverified assumptions as to the regulatory functions and their dozens or hundreds of unknown parameters.
Gene regulatory network of cell differentiation in the development of Ascidiacea.

The original network includes 16 repressive self-loops removed as subsumed under degradation
1.) Remove repressive self-loops

\[
\frac{d(gene_2)}{dt} = k_{2,s} \cdot \frac{k_{2,1} \cdot gene_1}{1 + k_{2,1} \cdot gene_1} - k_{2,d} \cdot gene_2
\]

\[
\dot{x}_k = f_k(x_{I_k}) - d_k(x_k)
\]
1.) Remove repressive self-loops

\[ \frac{d(gene_2)}{dt} = k_{2,s} \cdot \frac{k_{2,1} \cdot gene_1}{1 + k_{2,1} \cdot gene_1} - k_{2,d} \cdot gene_2 \]

2.) Reduce network by successive removal of nodes without input or without output.

\[ \dot{x}_k = f_k(x_{I_k}) - d_k(x_k) \]

http://www.nature.com/nrm/journal/v9/n10/full/nrm2503.html
Reduced network obtained by successive removal of nodes without input or without output.
The idea: Control entire network via a few nodes
Feedback Vertex Sets (FVS) = a subset of vertices in a directed graph, such that the removal of the set leaves the graph without directed cycles.
80 genes

Feedback vertex set = 1 gene

7 genes
\[ x_{\text{Fox}} = h_{\text{Fox}}(x_{\text{Otx}}, x_{\text{Twist}}) \]
\[ x_{\text{FGF}} = h_{\text{FGF}}(x_{\text{Fox}}) \]
\[ x_{\text{nodal}} = h_{\text{nodal}}(x_{\text{Fox}}, x_{\text{FGF}}) \]
\[ x_{\text{NoTrlc}} = h_{\text{NoTrlc}}(x_{\text{nodal}}, x_{\text{Fox}}, x_{\text{FGF}}) \]
\[ x_{\text{Otx}} = h_{\text{Otx}}(x_{\text{FGF}}) \]
\[ x_{\text{Twist}} = h_{\text{Twist}}(x_{\text{NoTrlc}}, x_{\text{Fox}}, x_{\text{FGF}}, x_{\text{Otx}}, x_{\text{ZicL}}) \]
\[ x_{\text{ZicL}} = h_{\text{ZicL}}(x_{\text{Fox}}, x_{\text{FGF}}) \]
$$x_{Fox} = h_{Fox}(h_{Otx}(h_{FGF}(x_{Fox})), h_{Twist}(h_{NoTrlc}(h_{nodal}(x_{Fox}, h_{FGF}(x_{Fox}))), x_{Fox}, h_{FGF}(x_{Fox}))), x_{Fox}, h_{FGF}(x_{Fox}), h_{Otx}(h_{FGF}(x_{Fox})), h_{ZicL}(x_{Fox}, h_{FGF}(x_{Fox}))))$$

$$x_{FGF} = h_{FGF}(x_{Fox})$$

$$x_{nodal} = h_{nodal}(x_{Fox}, h_{FGF}(x_{Fox}))$$

$$x_{NoTrlc} = h_{NoTrlc}(h_{nodal}(x_{Fox}, h_{FGF}(x_{Fox})), x_{Fox}, h_{FGF}(x_{Fox}))$$

$$x_{Otx} = h_{Otx}(h_{FGF}(x_{Fox}))$$

$$x_{Twist} = h_{Twist}(h_{NoTrlc}(h_{nodal}(x_{Fox}, h_{FGF}(x_{Fox}))), x_{Fox}, h_{FGF}(x_{Fox})), x_{Fox}, h_{FGF}(x_{Fox}), h_{Otx}(h_{FGF}(x_{Fox})), h_{ZicL}(x_{Fox}, h_{FGF}(x_{Fox}))))$$

$$x_{ZicL} = h_{ZicL}(x_{Fox}, h_{FGF}(x_{Fox}))$$
Does diversity of cell differentiation depend only on the activity of FoxD-a/b?
Does diversity of cell differentiation depend only on the activity of FoxD-a/b?

Check using biology data.

<table>
<thead>
<tr>
<th></th>
<th>FoxD-a/b</th>
<th>NoTrlc</th>
<th>Otx</th>
<th>Twist-like-1</th>
<th>ZicL</th>
</tr>
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<tbody>
<tr>
<td>Palp</td>
<td>0</td>
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<tr>
<td>TLC</td>
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<td>1</td>
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<tr>
<td>TVC</td>
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<tr>
<td>Endoderm</td>
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</tr>
</tbody>
</table>
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<td>a-Line-lateral-epidermis</td>
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<td>Muscle</td>
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<td>Endoderm</td>
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</tbody>
</table>
Does diversity of cell differentiation depend only on the activity of FoxD-a/b?

Check using biology data if available.

If not, check using simulated data.

If it does not depend only on FoxD-a/b, then regulatory network is incorrect.

Regulatory networks are possibly incomplete. We can never exclude the possibility that unknown species of molecules or unknown regulations may have an important role.
Assume

\[ g_{j \rightarrow k}^s(x) = \begin{cases} 
0.1 & (0 \leq x < 0.2) \\
0.3 & (0.2 \leq x < 0.4) \\
0.5 & (0.4 \leq x < 0.6) \\
0.7 & (0.6 \leq x < 0.8) \\
0.9 & (0.8 \leq x)
\end{cases} \]

or

\[ g_{j \rightarrow k}^c(x) = 1 \]

\[ f_k = \prod_{j \in I_k} g_{j \rightarrow k}(x_j) \]

\[ \dot{x}_k = f_k(x_{I_k}) - x_k \]
Trials: 1000 sets of random choices of regulatory functions, and 1000 different initial states for each set of functions.
$$g_{j \to k}(x_j) = \begin{cases} 
0.5 & (0 \leq x < T_{j \to k}) \\
1.0 & (T_{j \to k} \leq x) 
\end{cases}$$
Does diversity of cell differentiation depend only on the activity of FoxD-a/b?

Check using biology data if available. If not check using simulated data.

If it does not depend only on FoxD-a/b, then regulatory network is incorrect.

Regulatory networks are possibly incomplete. We can never exclude the possibility that unknown species of molecules or unknown regulations may have an important role.
A feedback vertex set circled in red
Table 2
List of minimal feedback vertex sets of molecules in the signal transduction network. There are 36 possible choices of minimal feedback vertex set.

<table>
<thead>
<tr>
<th></th>
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<th># Combinations</th>
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<td>②</td>
<td>③</td>
<td>④</td>
<td>⑤</td>
<td>2 × 3 × 3 = 18</td>
</tr>
<tr>
<td>ErbB11</td>
<td>SOS</td>
<td>HB-EGF</td>
<td>cyt Ca$^{2+}$</td>
<td>PI4,5-P2</td>
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<td></td>
<td>CaM</td>
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<td>ERK1/2</td>
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<td>ErbB11</td>
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<td>HB-EGF</td>
<td>cyt Ca$^{2+}$</td>
<td>PI4-P</td>
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<td></td>
<td>DAG</td>
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<td>PKC</td>
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<td>PLD</td>
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<td>Phosphatidyl acid</td>
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<td>PI5K</td>
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<td>3 × 6 = 18</td>
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<td>4</td>
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<tr>
<td>1</td>
<td>ErbB11</td>
<td>SOS</td>
<td>c-Src</td>
<td>cyt Ca²⁺</td>
<td>PI4,5-P2</td>
</tr>
<tr>
<td>2</td>
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<td>SOS</td>
<td>HB-EGF</td>
<td>cyt Ca²⁺</td>
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<td>cyt Ca²⁺</td>
<td>ADAMS</td>
</tr>
</tbody>
</table>

ADAMS
Phosphatidyl acid
PI5K
Reduced dynamical system of mammalian circadian rhythms

21 nodes
21 variables & 21 differential equations
21 variables & 21 differential equations

FVS has 7 nodes; controlling these 7 variables = control of entire network
\[
\frac{d\text{Per2}}{dt} = \left( v_{0,\text{Per2}} + v_{1,\text{Per2}} \cdot \frac{\text{CLK/BMAL1}^{n_{a1,\text{Per2}}}}{K_A^{n_{a1,\text{Per2}}} + \text{CLK/BMAL1}^{n_{a1,\text{Per2}}}} \right) \\
\times \frac{K_I^{n_{i1,\text{Per2}}}}{K_I^{n_{i2,\text{Per2}}} + \text{PER1/CYR1}^{n_{i1,\text{Per2}}}} \cdot \frac{K_I^{n_{i2,\text{Per2}}}}{K_I^{n_{i3,\text{Per2}}} + \text{PER2/CYR1}^{n_{i2,\text{Per2}}}} \cdot \frac{K_I^{n_{i3,\text{Per2}}}}{K_I^{n_{i4,\text{Per2}}} + \text{PER2/CYR2}^{n_{i3,\text{Per2}}}} \cdot \frac{K_I^{n_{i4,\text{Per2}}}}{K_I^{n_{i1,\text{Per2}}} + \text{PER2/CYR2}^{n_{i4,\text{Per2}}}} \\
- k_{m,\text{Per2}} \cdot \text{Per2}
\]
hundreds of variables

\[
\begin{align*}
v_{0,\text{Per1}} &= 0.000001, \quad v_{1,\text{Per1}} = 3.0, \quad v_{0,\text{Per2}} = 0.09, \quad v_{1,\text{Per2}} = 3.29, \\
v_{0,\text{Cry1}} &= 0.26, \quad v_{1,\text{Cry1}} = 2.44, \quad v_{2,\text{Cry1}} = 2.89, \quad v_{0,\text{Cry2}} = 1.29, \\
v_{1,\text{Cry2}} &= 2.72, \quad v_{2,\text{Cry2}} = 0.1, \quad v_{1,\text{Rev--erba}} = 11.06, \quad v_{0,\text{Clk}} = 3.98, \\
v_{1,\text{Clk}} &= 3.36, \quad v_{0,\text{Bmal1}} = 1.98, \quad v_{1,\text{Bmal1}} = 4.12, \quad v_{0,\text{Rorc}} = 0.06, \\
v_{1,\text{Rorc}} &= 3.55, \quad v_{2,\text{Rorc}} = 0.46. \\
\end{align*}
\]

\[
\begin{align*}
n_{a1,\text{Per1}} &= 2.0, \quad n_{i1,\text{Per1}} = 2.0, \quad n_{i2,\text{Per1}} = 1.0, \quad n_{i3,\text{Per1}} = 2.0, \\
n_{i4,\text{Per1}} &= 4.0, \quad n_{a1,\text{Per2}} = 10.0, \quad n_{i1,\text{Per2}} = 1.0, \quad n_{i2,\text{Per2}} = 1.0, \\
n_{i3,\text{Per2}} &= 9.0, \quad n_{i4,\text{Per2}} = 8.0, \quad n_{a1,\text{Cry1}} = 4.91, \quad n_{a2,\text{Cry1}} = 3.01, \\
n_{i1,\text{Cry1}} &= 1.0, \quad n_{i2,\text{Cry1}} = 1.0, \quad n_{i3,\text{Cry1}} = 6.0, \quad n_{i4,\text{Cry1}} = 4.0, \\
n_{i5,\text{Cry1}} &= 2.24, \quad n_{a1,\text{Cry2}} = 4.39, \quad n_{a2,\text{Cry2}} = 4.43, \quad n_{i1,\text{Cry2}} = 1.0, \\
n_{i2,\text{Cry2}} &= 1.0, \quad n_{i3,\text{Cry2}} = 4.0, \quad n_{i4,\text{Cry2}} = 8.0, \quad n_{i5,\text{Cry2}} = 1.75, \\
n_{a1,\text{Rev--erba}} &= 4.40, \quad n_{i1,\text{Rev--erba}} = 0.15, \quad n_{i2,\text{Rev--erba}} = 0.3, \\
n_{i3,\text{Rev--erba}} &= 7.0, \quad n_{i4,\text{Rev--erba}} = 7.0, \quad n_{a1,\text{Clk}} = 3.50, \quad n_{i1,\text{Clk}} = 1.96, \\
n_{a1,\text{Bmal1}} &= 4.13, \quad n_{i1,\text{Bmal1}} = 0.02, \quad n_{a1,\text{Rorc}} = 1.57, \quad n_{a2,\text{Rorc}} = 0.56, \\
n_{i1,\text{Rorc}} &= 1.0, \quad n_{i2,\text{Rorc}} = 1.0, \quad n_{i3,\text{Rorc}} = 7.0, \quad n_{i4,\text{Rorc}} = 7.0, \quad n_{i5,\text{Rorc}} = 4.33. \\
K_{A1,\text{Per1}} &= 1.98, \quad K_{I1,\text{Per1}} = 1.07, \quad K_{I2,\text{Per1}} = 3.96, \quad K_{I3,\text{Per1}} = 1.68, \\
K_{I4,\text{Per1}} &= 3.11, \quad K_{A1,\text{Per2}} = 1.90, \quad K_{I1,\text{Per2}} = 4.51, \quad K_{I2,\text{Per2}} = 2.98, \\
K_{I3,\text{Per2}} &= 2.24, \quad K_{I4,\text{Per2}} = 3.31, \quad K_{A1,\text{Cry1}} = 1.46, \quad K_{A2,\text{Cry1}} = 3.76, \\
K_{I1,\text{Cry1}} &= 0.03, \quad K_{I2,\text{Cry1}} = 0.77, \quad K_{I3,\text{Cry1}} = 3.59, \quad K_{I4,\text{Cry1}} = 3.44, \\
K_{I5,\text{Cry1}} &= 2.82, \quad K_{A1,\text{Cry2}} = 0.69, \quad K_{A2,\text{Cry2}} = 2.96, \quad K_{I1,\text{Cry2}} = 4.63, \\
K_{I2,\text{Cry2}} &= 2.95, \quad K_{I3,\text{Cry2}} = 3.57, \quad K_{I4,\text{Cry2}} = 2.75, \quad K_{I5,\text{Cry2}} = 3.97, \\
K_{A1,\text{Rev--erba}} &= 3.15, \quad K_{I1,\text{Rev--erba}} = 3.56, \quad K_{I2,\text{Rev--erba}} = 3.62, \\
K_{I3,\text{Rev--erba}} &= 4.71, \quad K_{I4,\text{Rev--erba}} = 1.23, \quad K_{A1,\text{Clk}} = 1.59, \quad K_{I1,\text{Clk}} = 0.83, \\
K_{A1,\text{Bmal1}} &= 2.59, \quad K_{I1,\text{Bmal1}} = 2.47, \quad K_{A1,\text{Rorc}} = 4.30, \quad K_{A2,\text{Rorc}} = 4.89, \\
K_{I1,\text{Rorc}} &= 3.49, \quad K_{I2,\text{Rorc}} = 2.34, \quad K_{I3,\text{Rorc}} = 2.71, \quad K_{I4,\text{Rorc}} = 2.09, \\
K_{I5,\text{Rorc}} &= 3.36. \\
k_{m,\text{Per1}} &= 2.18, \quad k_{m,\text{Per2}} = 0.20, \quad k_{m,\text{Cry1}} = 0.22, \quad k_{m,\text{Cry2}} = 0.41, \\
k_{m,\text{Rev--erba}} &= 0.60, \quad k_{m,\text{Clk}} = 3.19, \quad k_{m,\text{Bmal1}} = 1.42, \quad k_{m,\text{Rorc}} = 1.50, \\
k_{p,\text{PER1}} &= 2.58, \quad k_{p,\text{PER2}} = 3.0, \quad k_{p,\text{Cry1}} = 0.312, \quad k_{p,\text{Cry2}} = 5.9, \\
k_{p,\text{REV--ERBA}} &= 0.31, \quad k_{p,\text{CLK}} = 1.52, \quad k_{p,\text{BMAL1}} = 2.28, \quad k_{p,\text{RORC}} = 3.33, \\
t_{\text{Per1}} &= 3.05, \quad t_{\text{Per2}} = 2.38, \quad t_{\text{Cry1}} = 3.94, \quad t_{\text{Cry2}} = 1.69, \quad t_{\text{Rev--erba}} = 1.60, \\
t_{\text{Clk}} &= 3.04, \quad t_{\text{Bmal1}} = 4.00, \quad t_{\text{Rorc}} = 1.39, \quad a_{\text{PER1,Cry1}} = 3.57, \\
a_{\text{PER1,Cry2}} &= 3.12, \quad a_{\text{PER2,Cry1}} = 3.81, \quad a_{\text{PER2,Cry2}} = 4.0, \quad a_{\text{CLK,BMAL1}} = 1.98, \quad a_{\text{PER1,Cry1}} = 1.32, \quad a_{\text{PER1,Cry2}} = 1.85, \quad a_{\text{PER2,Cry1}} = 1.37, \\
a_{\text{PER2,Cry2}} &= 2.42, \quad d_{\text{CLK/BMAL1}} = 0.97.
\]
Reduced dynamical system of mammalian circadian rhythms

21 nodes
Identified small feedback vertex sets (FVS), by measurements of which any recurrent dynamical behavior of whole system is assured to be identified.

If it does not depend only on FVS, then regulatory network is incorrect.

Have a rational criterion to select key molecules to control a system: the dynamics of whole system is sufficiently controlled by prescribing the dynamics on a FVS.
Complex network structure frequently appear in biological systems such as gene regulatory networks, circadian rhythm models, signal transduction circuits, etc. As a mathematical formulation of such biological complex network systems, Fiedler, Mochizuki and their collaborators (JDDE 2013) recently defined a class of ODEs associated with a finite digraph called a regulatory network, and proved that its dynamics on the global attractor can in principle be faithfully monitored by information from a (potentially much) fewer number of nodes called the feedback vertex set of the graph. In this talk, I will use their theory to give a method for detecting a more detailed information on the dynamics of regulatory networks, namely the Morse decomposition of its global attractor. The main idea is to take time series data from the feedback vertex set of a regulatory network, and construct a combinatorial multi-valued map, to which we apply the so-called Conley-Morse Database method. As a test example, we study Mirsky’s mathematical model for mammalian circadian rhythm which can be represented as a regulatory network with 21 nodes, and show that numerically generated time series data from its feedback vertex set consisting of 7 nodes correctly detect a Morse decomposition in the global attractor, including 1 stable periodic orbit, 2 unstable periodic orbits, and 1 unstable fixed point. This is a joint work with B. Fielder, A. Mochizuki, G. Kurosawa, and H. Oka.
\[ f: X \times \Lambda \rightarrow X \]
\[ f(x, \lambda) = f_\lambda(x) \]
where \( X \) = phase space
\( \Lambda \) = parameter space

Example: A Leslie population model
\[ g([x_1, x_2]) \rightarrow [ (\theta_1 x_1 + \theta_2 x_2)e^{-0.1(x_1 + x_2)}, px_1 ] \]
\[ f( [x_1, x_2], [\theta_1, \theta_2, p] ) \rightarrow [ (\theta_1 x_1 + \theta_2 x_2)e^{-0.1(x_1 + x_2)}, px_1 ] \]

Defn: \( Z \subseteq X \) is invariant at \( \lambda \) if \( f_\lambda(Z) = Z \)
\( F: X \times \Lambda \rightarrow X \times \Lambda \)

\[ f(x, \lambda) = (f_\lambda(x), \lambda) \]

where \( X = \) phase space

\( \Lambda = \) parameter space

Defn: \( Z \subset X \) is invariant at \( \lambda \) if \( f_\lambda(Z) = Z \)

For \( \Lambda_0 \subset \Lambda \), let \( F_{\Lambda_0}: X \times \Lambda_0 \rightarrow X \times \Lambda_0 \)

For \( S \subset X \times \Lambda \), let \( S_{\Lambda_0} = S \cap (X \times \Lambda_0) \)

\( S \subset X \times \Lambda \) is invariant over \( \Lambda_0 \) if \( F_{\Lambda_0}(S_{\Lambda_0}) = S_{\Lambda_0} \)
$N \subset X \times \Lambda_0$ is an isolating neighborhood for if

$$\text{Inv}(N, F_{\Lambda_0}) \subset \text{int}_{X \times \Lambda_0}(N)$$

where $\text{Inv}(N,F_{\Lambda_0}) =$ maximal invariant set in $N$ under $F_{\Lambda_0}$