Systematic Innovation in Pharmaceutical Industry

David W. Conley

BS, MBA

MATRIZ Level 4 Specialist

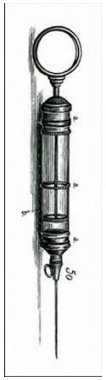
Agenda

- What is TRIZ?
- How are TRIZ and Systematic Innovation (SI) Used in the Pharmaceutical Industry?
- Which Pharma Companies Use TRIZ/SI?
- Back-up - What are TRIZ and Systematic Innovation (TRIZ/SI)?

What is TRIZ?

- TRIZ – The Theory of Inventive Problem Solving
  - Science based on the historical trends found in the world wide patent database as reflected in the commercially successful advancement of technical systems



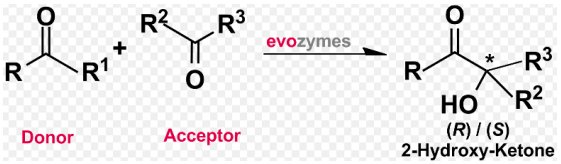




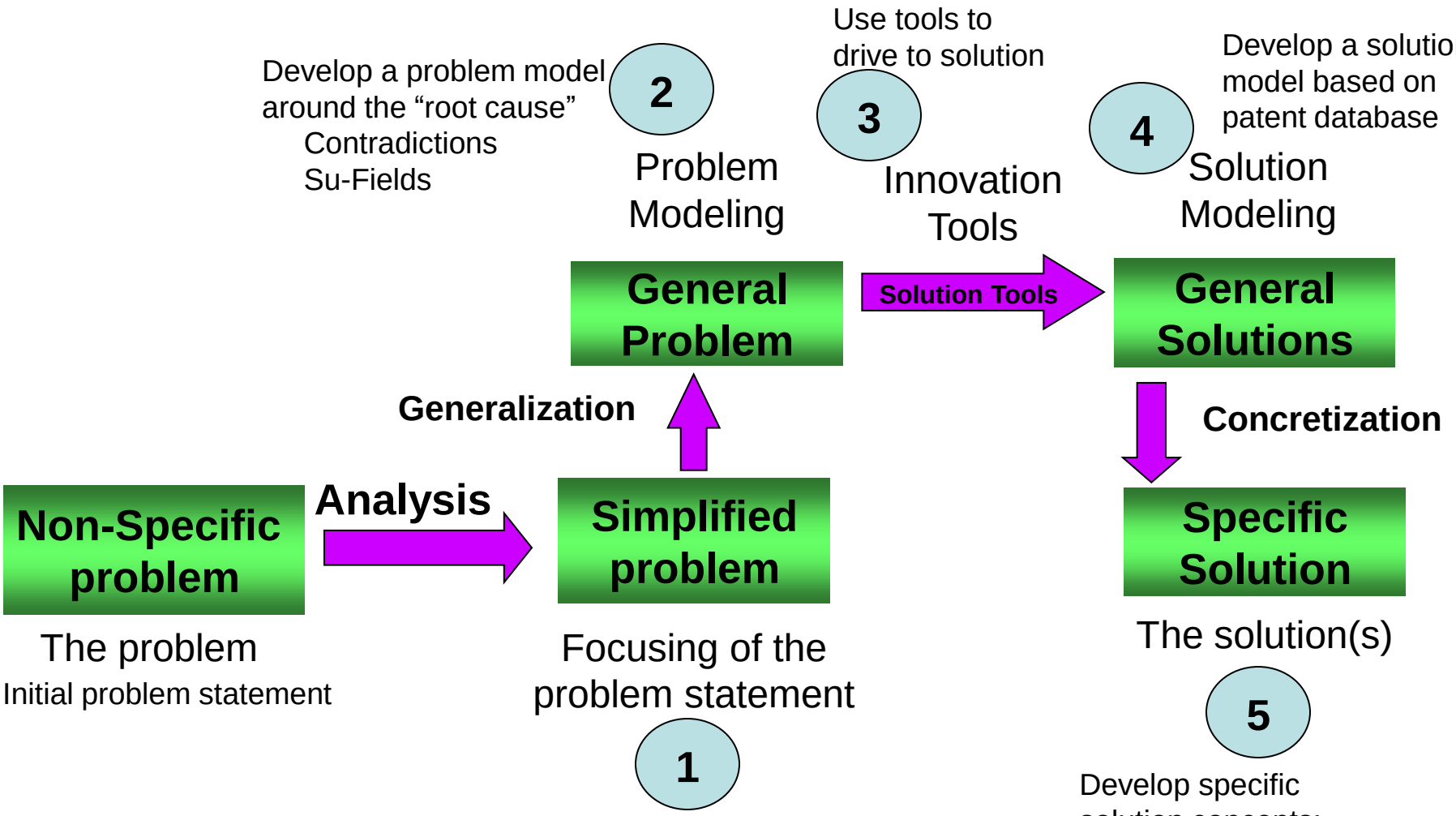
  - Only problem solving methodology that has hard (*vs. soft – e.g. brainstorming, design thinking, etc.*) solution development tool sets

Though the initial research leading to the development of TRIZ was based on electro-mechanical/thermal systems it has since been shown that it woks on any type of system.

System – a set of interaction components that create a function (or output)



What is TRIZ? - Innovation Process Map



How are TRIZ/SI Used in the Pharmaceutical Industry?

- TRIZ/SI usage in the pharmaceutical industry covers a wide range of applications:
  1. Active ingredient/functi… …teraction analysis
  2. Functional a… …nteraction with tar… …get biological components
  3. …g analysis of treatment delivery options
  4. Packaging (delivery mode) innovation
  5. Pharmaceutical manufacturing process improvement
  6. Analysis and improvement of research and business process methodologies.

Comprehensive set of tools and methods for effectively innovating a wide variety of challenges

How are TRIZ/SI Used in the Pharmaceutical Industry?

- TRIZ/SI usage in the pharmaceutical industry covers a wide range of applications:
  1. Active ingredient/functional interaction analysis
  2. System analysis of drug interaction with target and non-target biological components

Examples:

- Innovation direction for aspirin side effects
- Innovation direction for addressing antimicrobial resistance
- Back-up
  - Innovation direction for improvement of SSRI antidepressant
  - Innovation direction drill down for neurotransmitter functioning

How are TRIZ/SI Used in the Pharmaceutical Industry?

Non-Specific problem

The problem

Initial problem statement

•Innovation direction for aspirin side effects

How Aspirin Works

- Damaged tissue releases a chemical (prostaglandin) that makes nerve endings transmit pain signals at a higher level. The tissue makes the prostaglandin using an enzyme called cyclooxygenase 2 (COX-2).

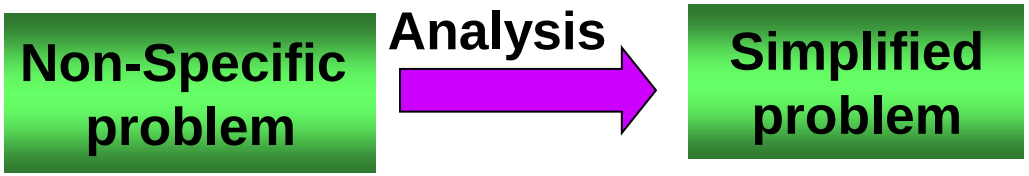
Non-Specific problem

The problem

Initial problem statement

Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects



The problem

Initial problem statement

Focusing of the problem statement

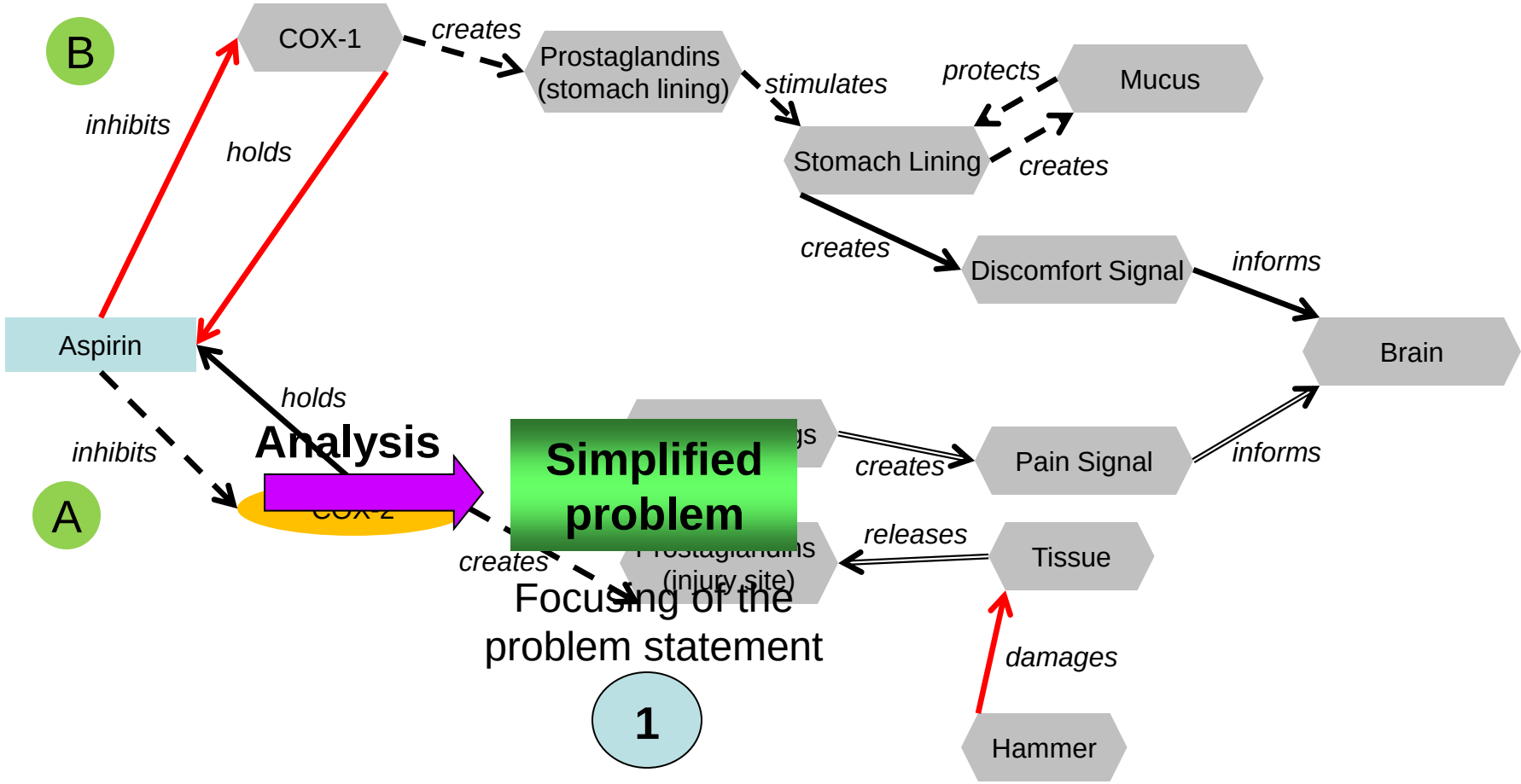
1

Restate the problem focusing on the root cause of the problem

- System analysis
- Cause and effect

Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects



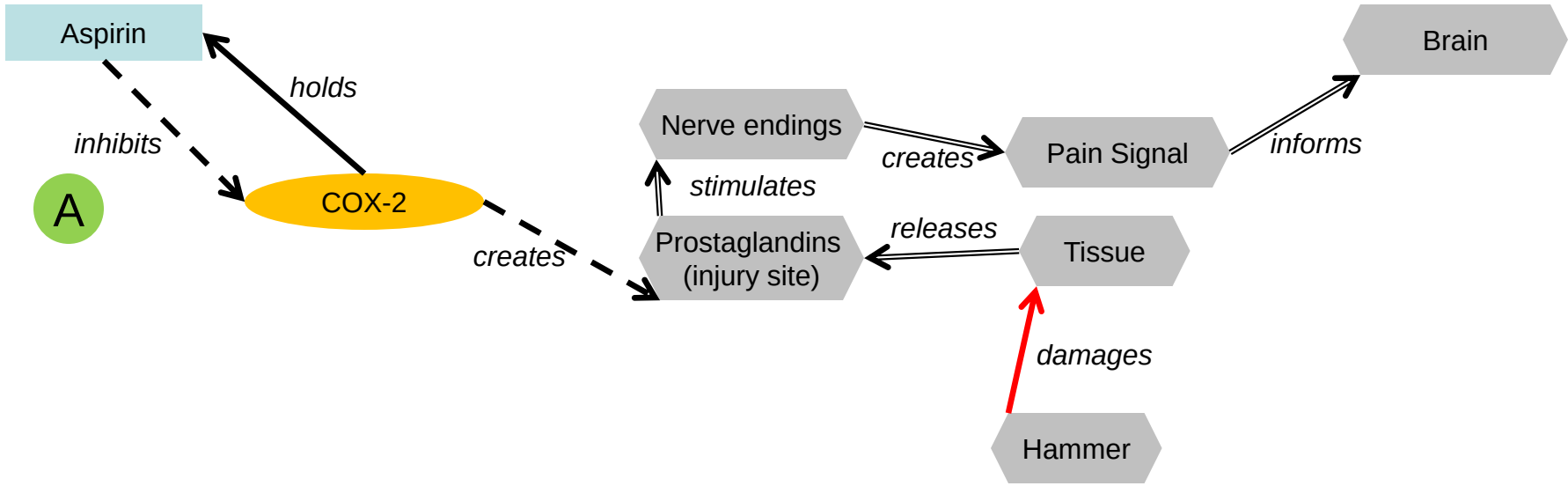
Restate the problem focusing on the root cause of the problem

- System analysis
- Cause and effect

Innovation Case Study – *Aspirin*

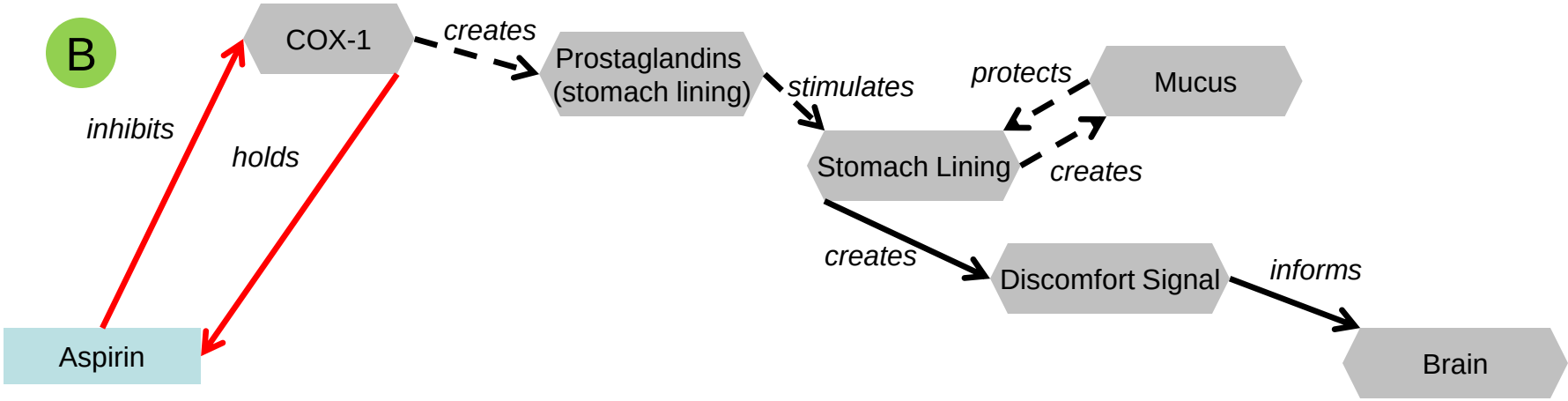
•Innovation direction for aspirin side effects

Need to maintain or enhance positive effect of aspirin



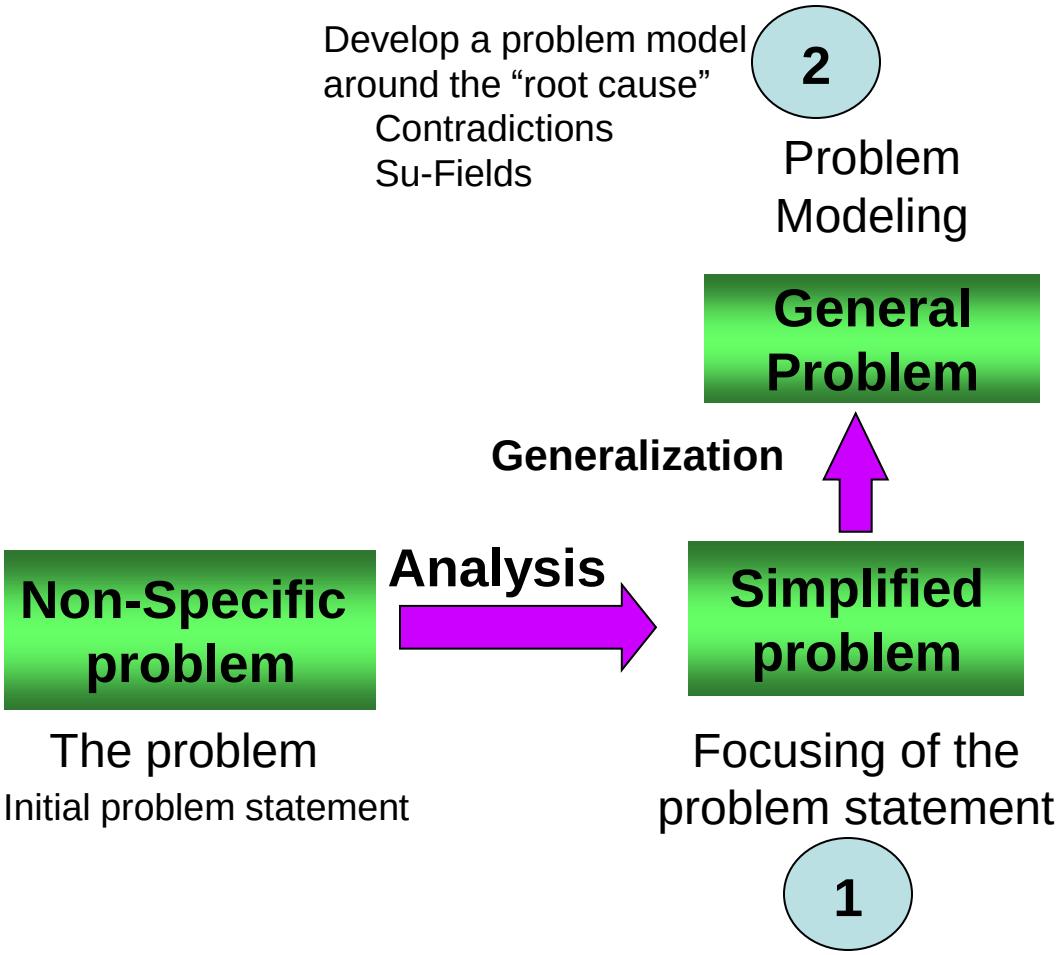
Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects

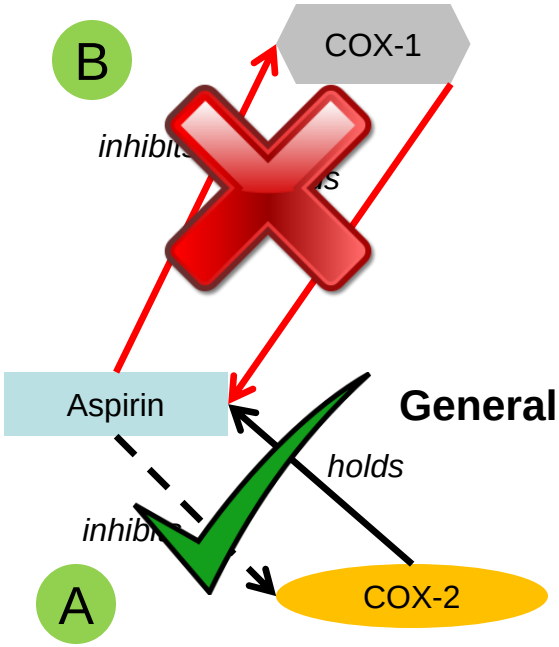


Need to stop or reduce negative effect of aspirin

Innovation Case Study – *Aspirin*



Innovation Case Study – *Aspirin*



Generalization

- Innovation direction for aspirin side effects

2

Problem Modeling

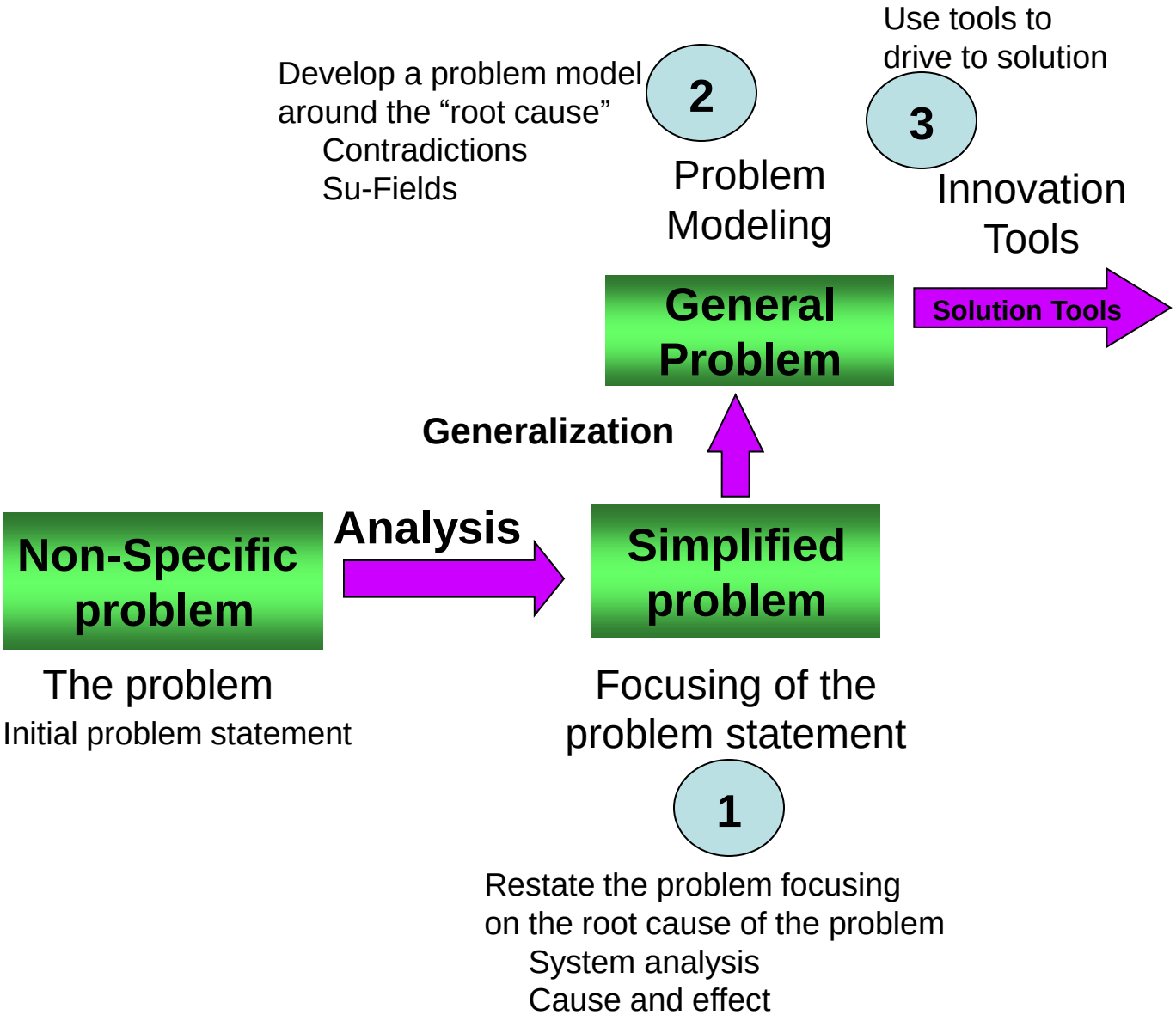
General Problem

tion Statement:

n to effect the body in order to reduce pain sensation

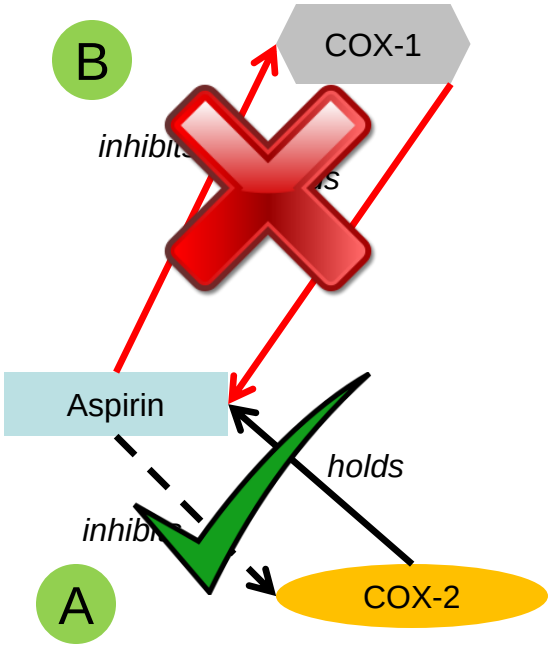
Do not want aspirin to effect the body in order to keep stomach lining healthy

Innovation Case Study – *Aspirin*



Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects



3

Innovation Tools

Contradiction:

✓ Want aspirin to effect the body in order to reduce pain sensation

✗ Do not want aspirin to effect the body in order to keep stomach lining healthy

This contradiction can be separated in 2 distinct ways:

1.) Space

-Where do we want aspirin to effect the body? At the point of injury

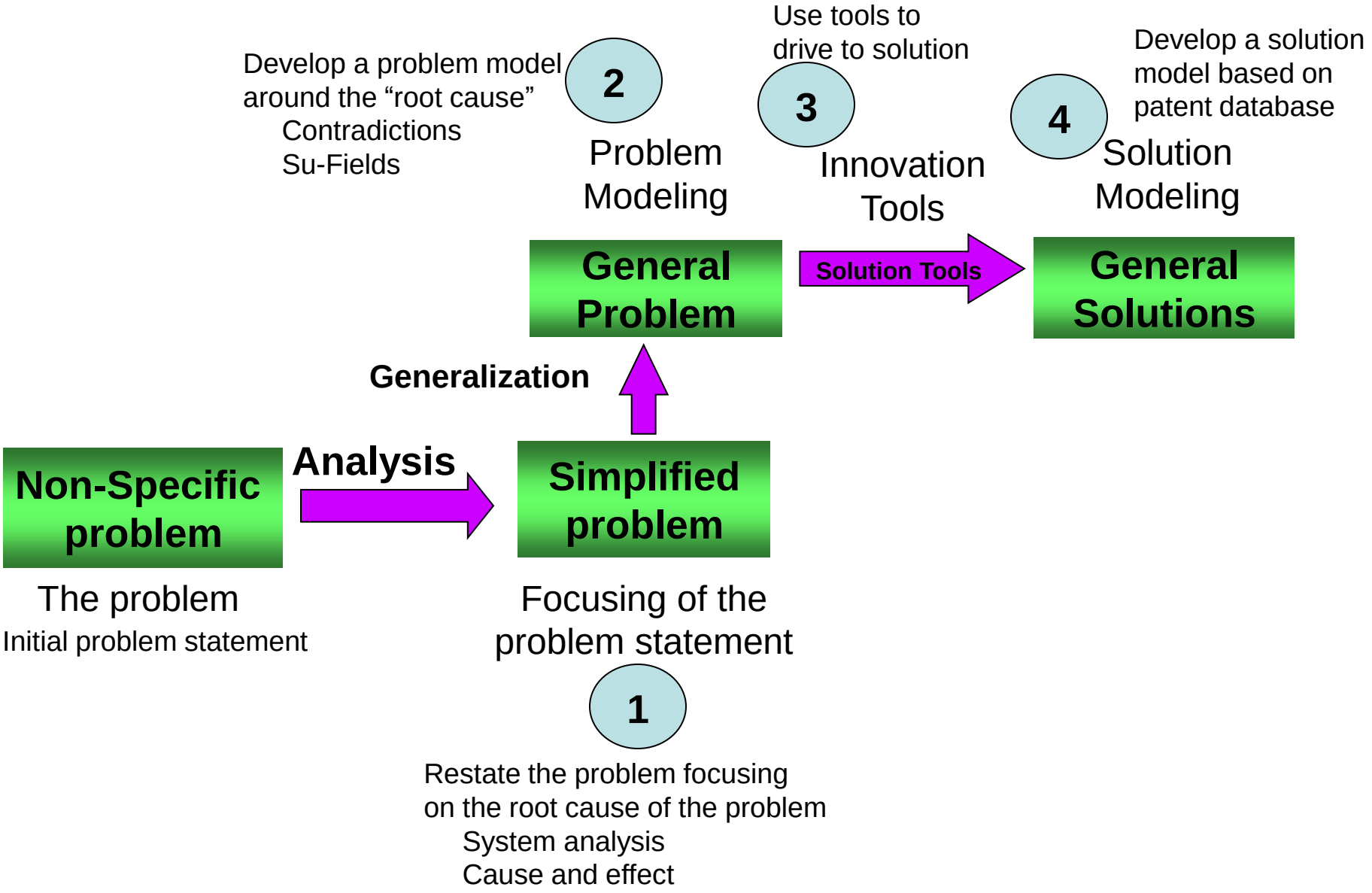
-Where do we not want aspirin to effect the body? In the stomach

2.) Relation

-In relation to what do we want the aspirin to effect the body? COX-2

-In relation to what do we not want the aspirin to effect the body? COX-1

Innovation Case Study – *Aspirin*



Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects

Develop a solution model based on patent database

4 Solution Modeling

General Solutions

Inventive Principles for Use in Separation in Space Strategies:

Separation in Space - Inventive Principles
1. Segmentation
2. Taking Out
3. Local Quality
7. "Nested Doll"
4. Asymmetry
17. Another Dimension

Nested doll – Put the drug inside another functioning material
- Non-reactive coating

Local quality – Have the drug behave differently when exposed to different chemistries
- Coating that reacts with chemistry outside of stomach

Another dimension – Apply the solution at a much smaller scale
- Utilize nano-scale delivery

Combined Solution – Utilize nano-particles as a coating that are small enough to be immediately absorbed by small intestines that will not activate until exposed to blood chemistry.

Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects

Inventive Principles for Use in Separation in Relation Strategies:

Separation in Relation - Inventive Principles
40. Composite Materials
31. Porous Materials
32. Color (Optical Property) Changes
3. Local Quality
19. Periodic Action
17. Another Dimension

Composite materials – Combine the drug with other materials
- Place the aspirin inside another device

Porous materials – Pace the drug in a porous material
- Utilize a porous device to release the drug

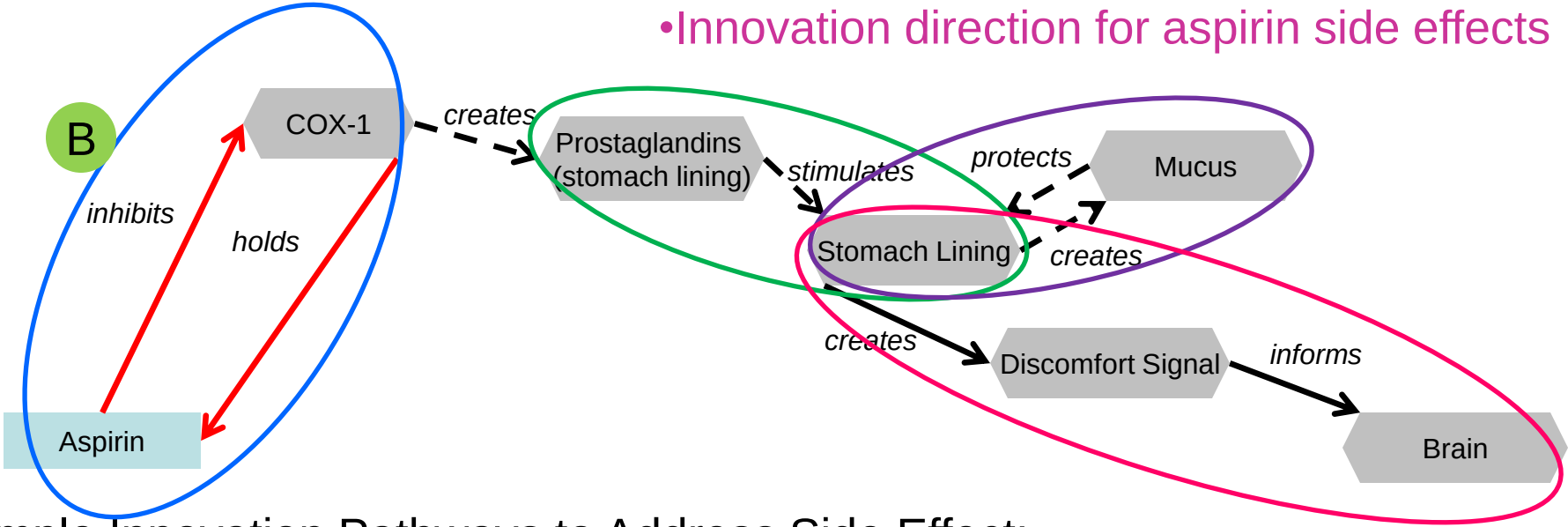
Local quality – Apply the drug where needed
- Place the device at the site of injury

Periodic action – Apply the drug periodically
- Release the aspirin in burst over time

Combined Solution – Utilize patch technology to deliver aspirin in bursts at the site of injury avoiding interaction with COX-1 in stomach. Patch could double as a protective adhesive strip when used at skin injury sites.

Innovation Case Study – *Aspirin*

•Innovation direction for aspirin side effects



Sample Innovation Pathways to Address Side Effect:

Inhibit aspirin from binding with COX-1

a. Occupy COX-1 binding sites with an inactive chemical
b. Render aspirin incapable of binding while in stomach
c. Reduce aspirin's capability for binding
d. Block interaction between COX-1 and aspirin

Improve ability of prostaglandin to stimulate mucus production

a. Accelerate production of prostaglandin in stomach
b. Improve ability of prostaglandin to stimulate lining

Drive alternative mucus production/effect

a. Find alternative stimulation of mucus production
b. Find alternative stomach lining protection

Mask symptoms

a. Block creating of "signal"
b. Block reception of "signal"

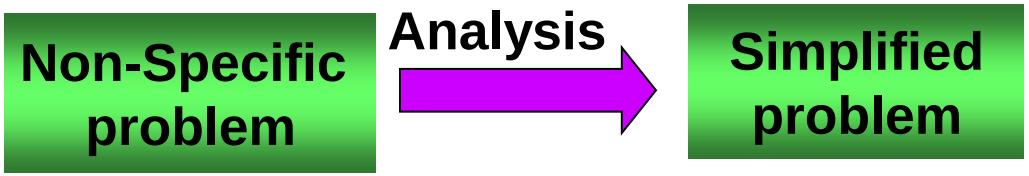
10 "location" opportunities for application of contradiction analysis in developing innovative solutions

Need to Address Antimicrobial Resistance

Non-Specific problem

The problem

Initial problem statement



The problem

Initial problem statement

Focusing of the problem statement

1

Restate the problem focusing on the root cause of the problem

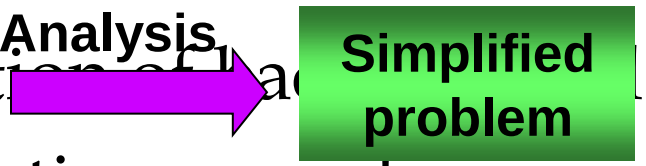
- System analysis
- Cause and effect

•Innovation direction for addressing antimicrobial resistance

How Bacteria Resist Antibiotics

- 4 primary mechanisms by which bacteria become antibiotic resistant

1. Drug inactivation or modification
2. Alterat[illegible]ing site
3. Antibiotic removal
4. Antibiotic blockage



Focusing of the problem statement

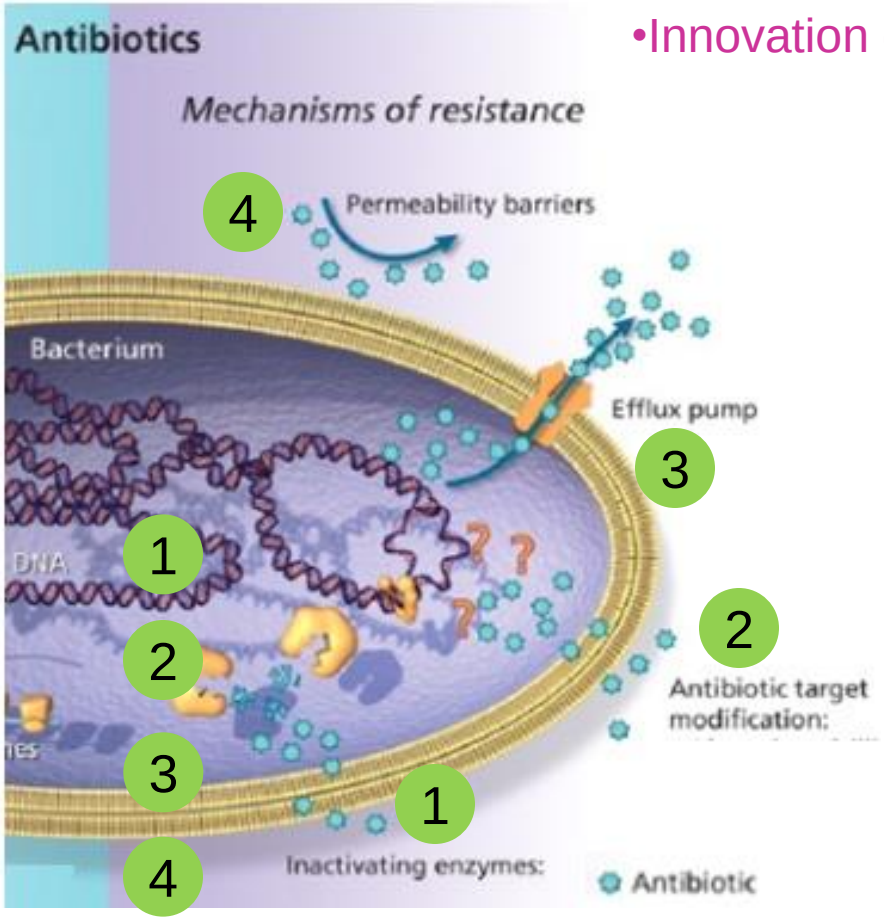
1

Restate the problem focusing on the root cause of the problem

System analysis

Cause and effect

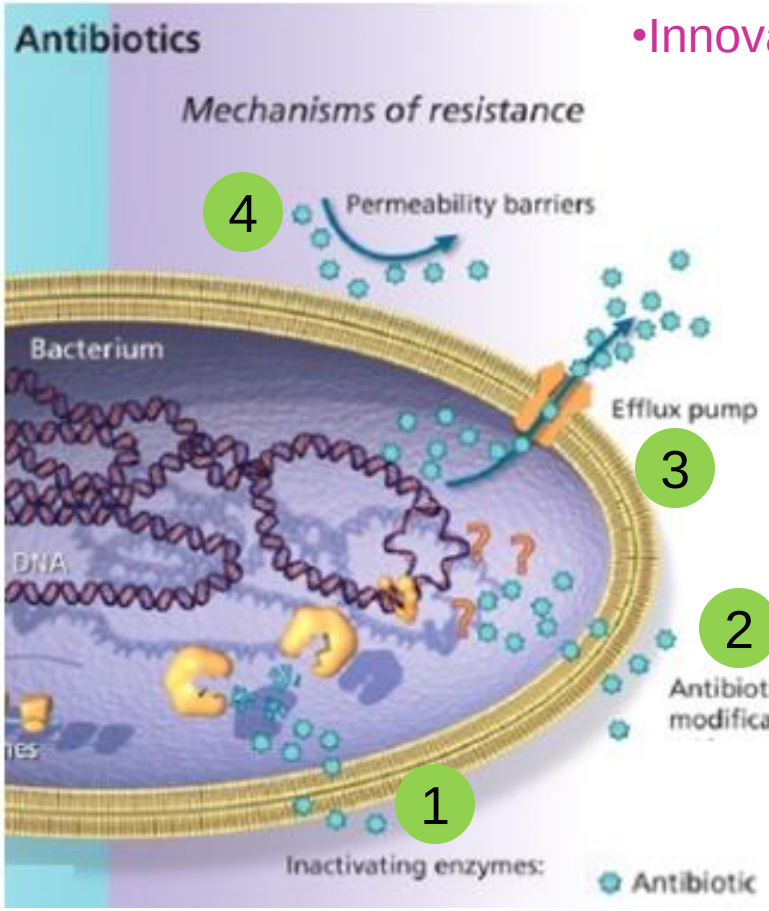
Innovation Case Study – *Antimicrobial Resistance*

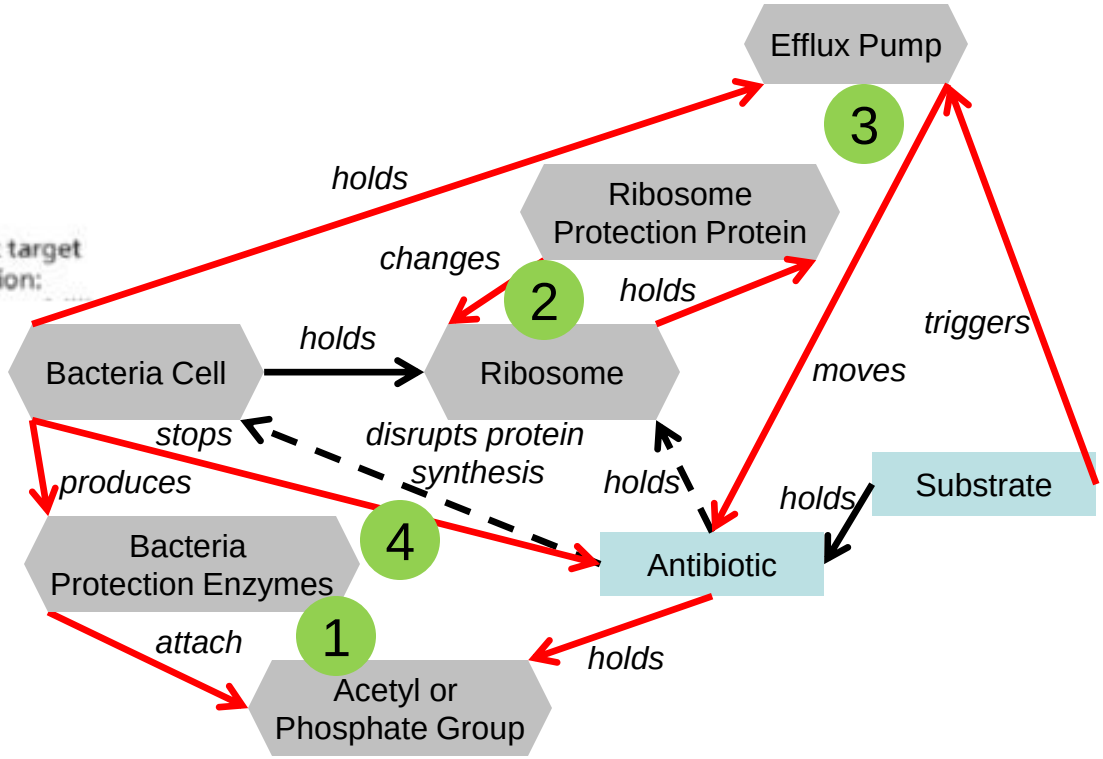


- Innovation direction for addressing antimicrobial resistance

Innovation Case Study – *Antimicrobial Resistance*

•Innovation direction for addressing antimicrobial resistance





Innovation Case Study – *Antimicrobial Resistance*

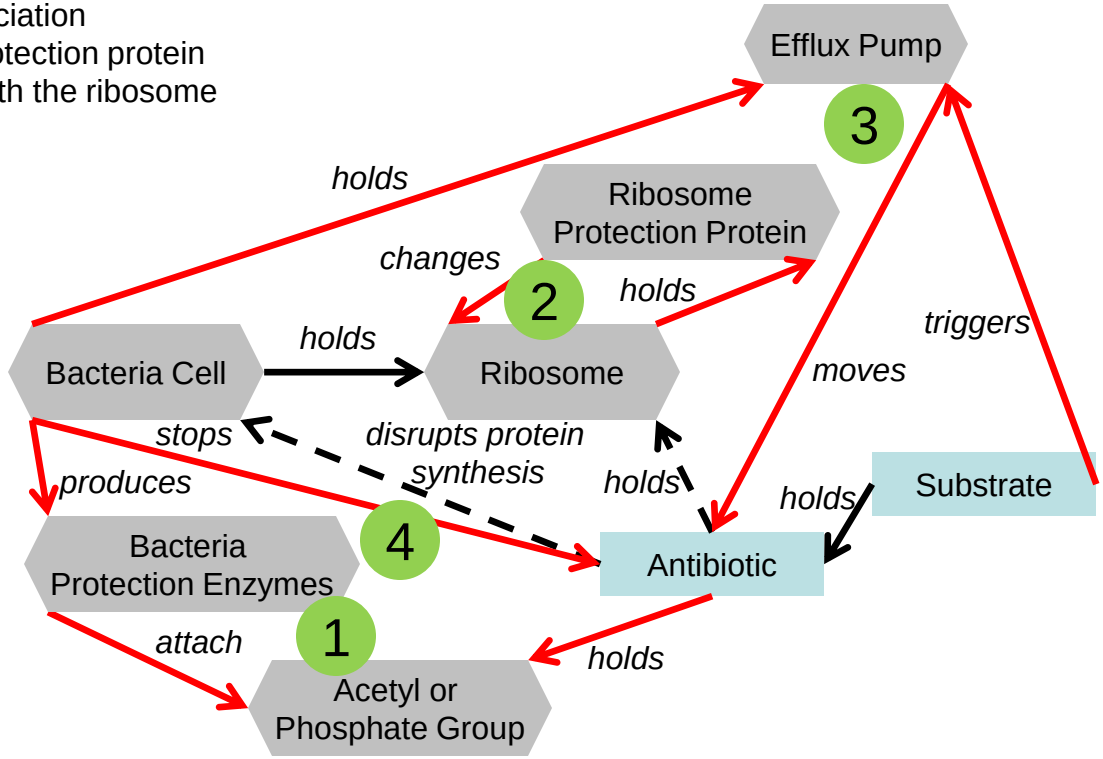
•Innovation direction for addressing antimicrobial resistance

1 **Stop drug modification or deactivation**
- a. stop bacteria from producing protection enzymes
- b. stop enzymes form attaching an acetyl group
- c. stop antibiotic from holding the acetyl group

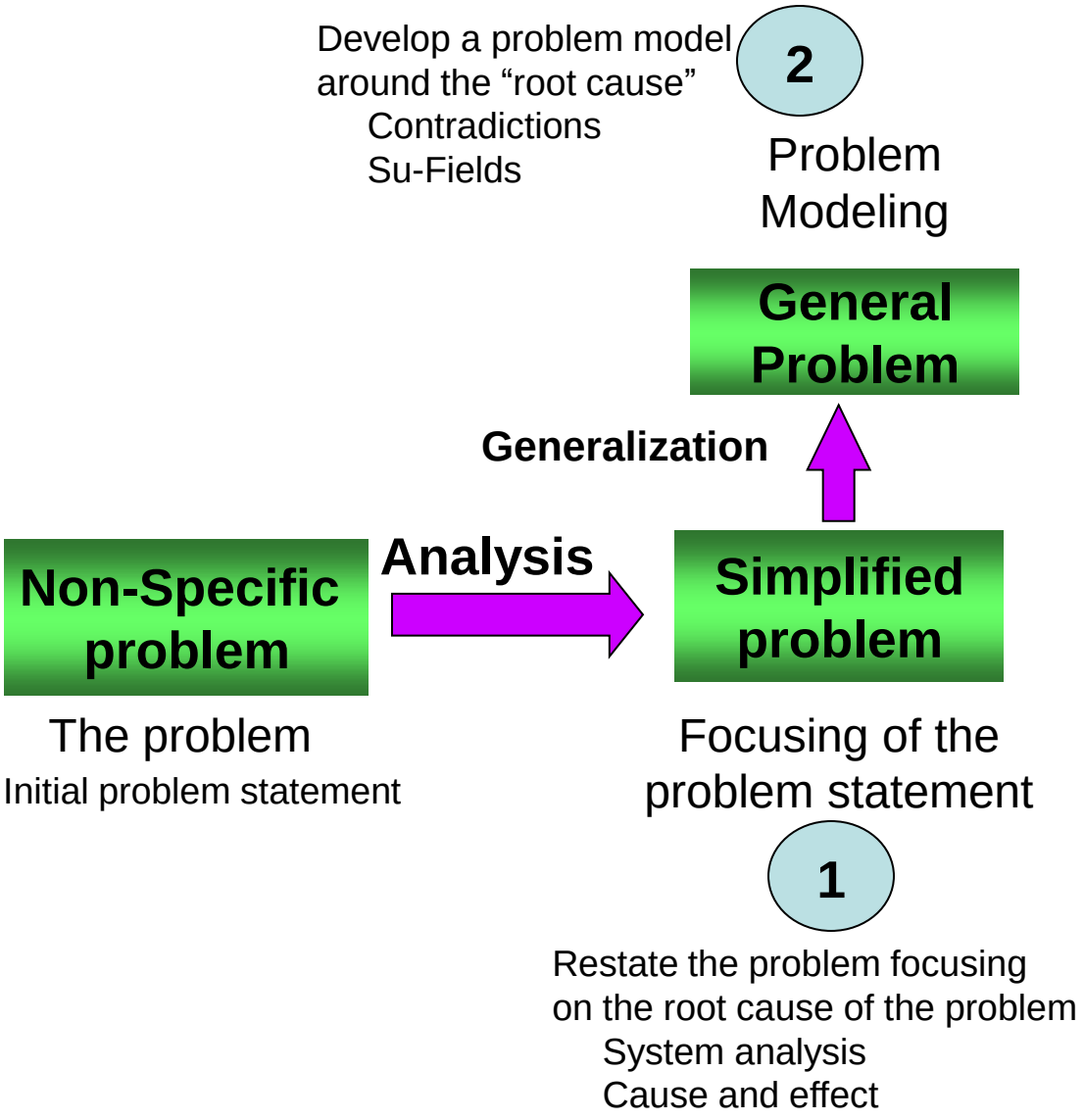
2 **Stop modification of bacteria binding site**
- a. disrupt the bacteria and ribosome association
- b. stop the connection of the ribosome protection protein
- c. create an antibiotic that can still bind with the ribosome

3 **Stop antibiotic removal**
- a. disrupt the function of the efflux pump
- b. stop the triggering of the efflux pump
- c. remove the efflux pump
- d. stop the interaction of the pump with the antibiotic

4 **Insure entrance of antibiotic into bacteria**
- a. increase permeability of bacteria cell
- b. reduce size of antibiotic
- c. Improve antibiotics penetration



Innovation Case Study – *Aspirin*



Innovation Case Study – *Antimicrobial Resistance*

•Innovation direction for addressing antimicrobial resistance

Develop a problem model around the "root cause"
Contradictions
Su-Fields

2

Problem Modeling

•If the antibiotic contains the necessary substrate then the antibiotic can effect the bacteria but the efflux pump can remove the antibiotic

•If the antibiotic does not contain the necessary substrate then the efflux pump can not remove it but the antibiotic ca… acteria

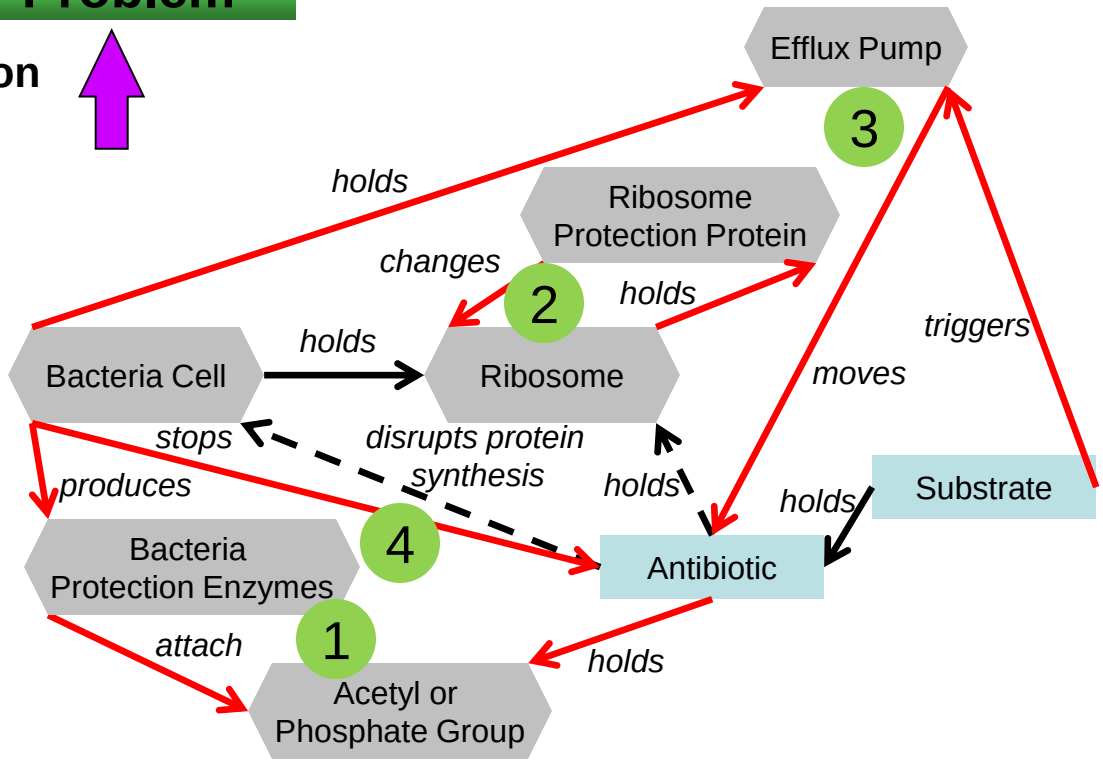
Abstracting the problem statement

General Problem

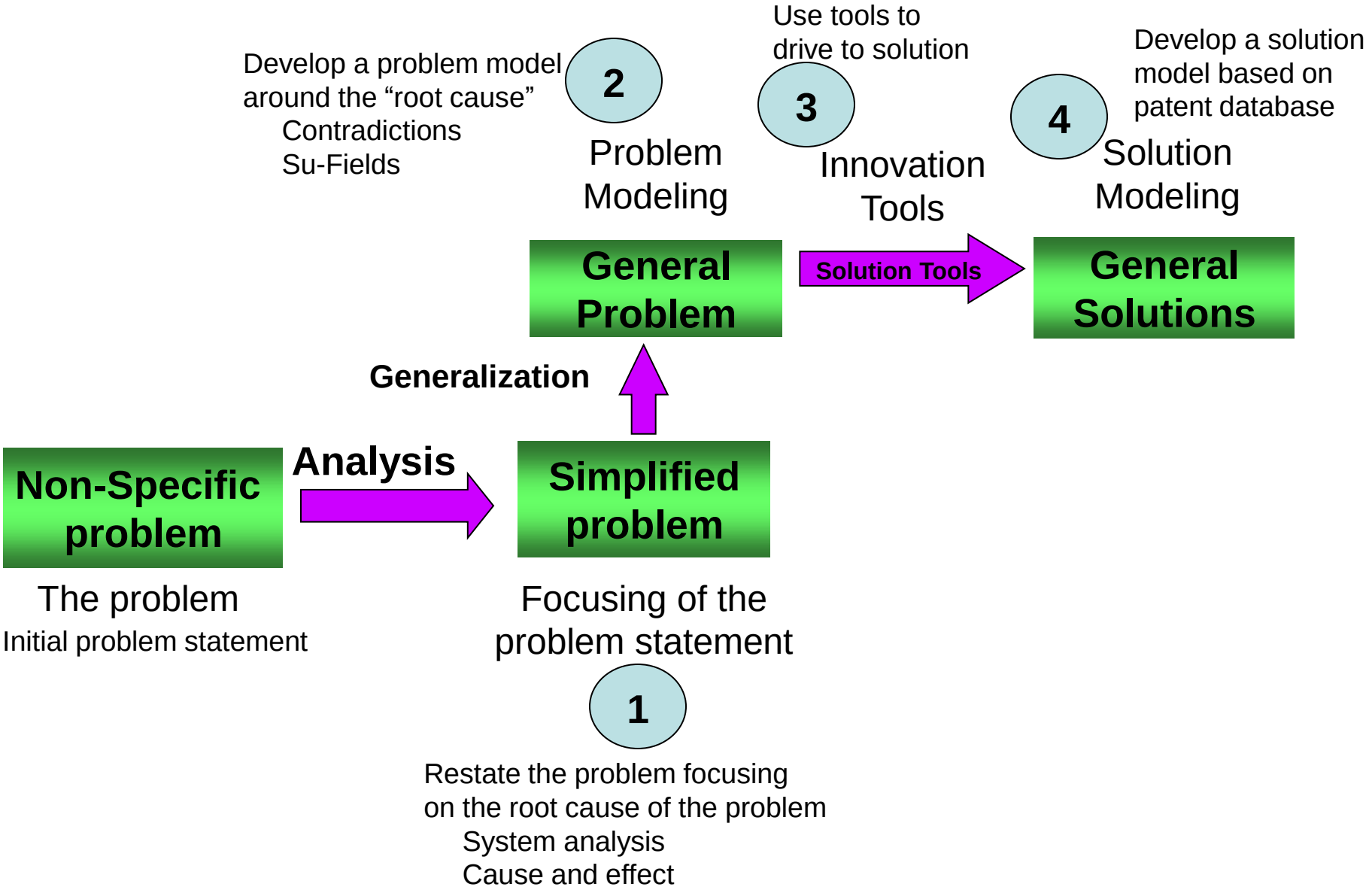
Generalization

3 **Stop antibiotic removal**

a. disrupt the function of the efflux pump
b. stop the triggering of the efflux pump
c. remove the efflux pump
d. stop the interaction of the pump with the antibiotic



Innovation Case Study – *Antimicrobial Resistance*



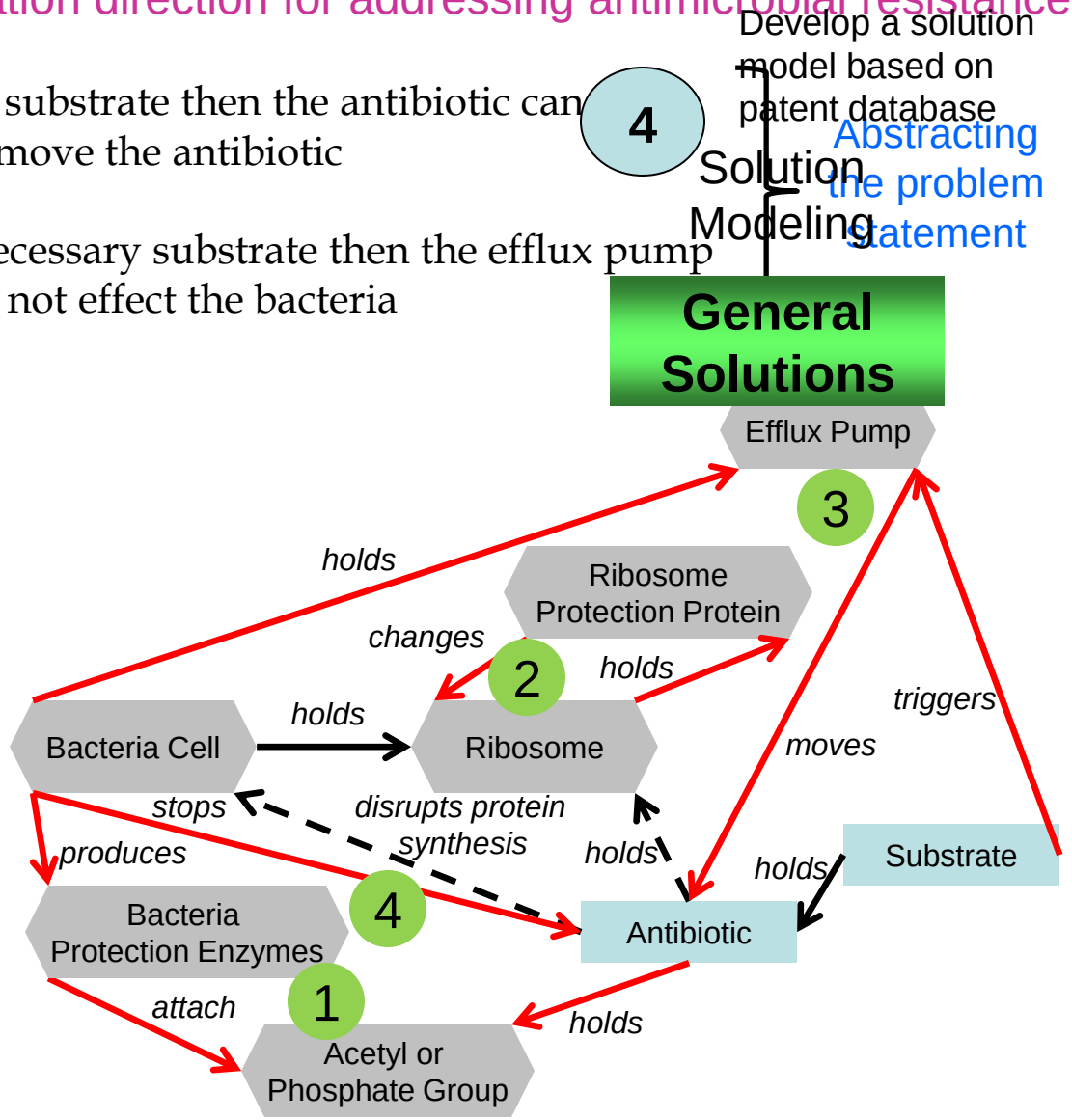
Innovation Case Study – *Antimicrobial Resistance*

•Innovation direction for addressing antimicrobial resistance

•If the antibiotic contains the necessary substrate then the antibiotic can the bacteria but the efflux pump can remove the antibiotic

•If the antibiotic does not contain the necessary substrate then the efflux pump can not remove it but the antibiotic can not effect the bacteria

Locally available resource analysis



Innovation Case Study – *Antimicrobial Resistance*

•Innovation direction for addressing antimicrobial resistance

•If the antibiotic contains the necessary substrate then the antibiotic can effect the bacteria but the efflux pump can remove the antibiotic

•If the antibiotic does not contain the necessary substrate then the efflux pump can not remove it but the antibiotic can not effect the bacteria

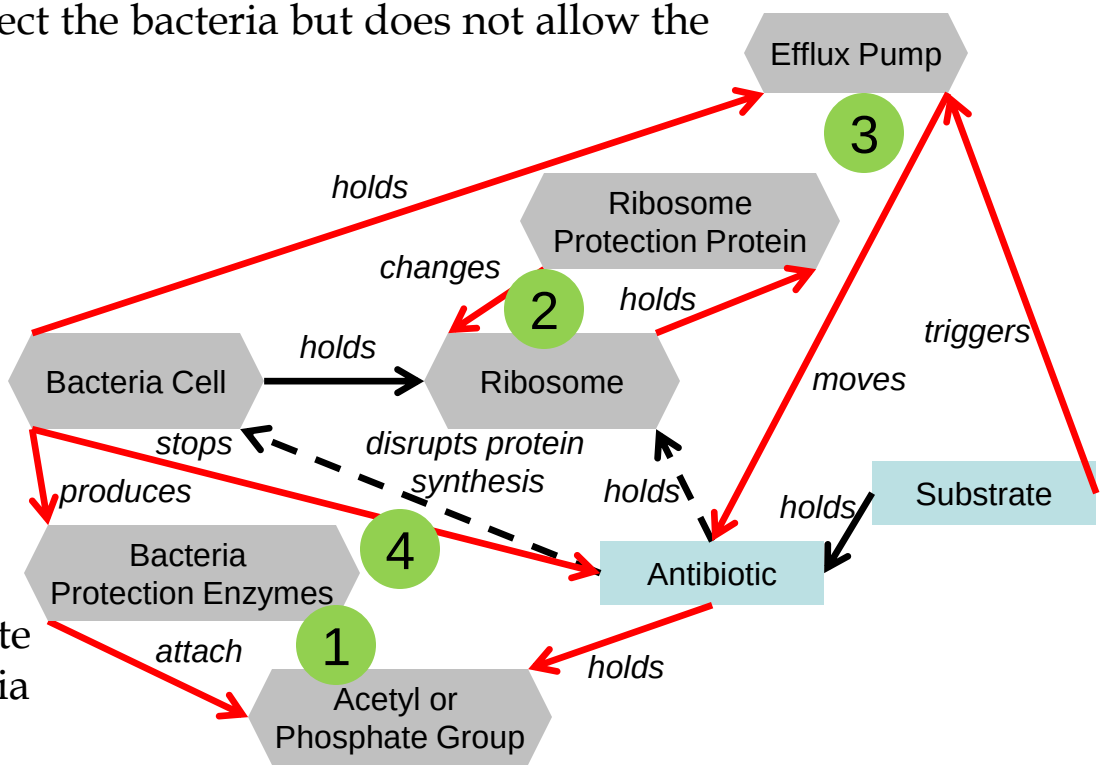
Abstracting the problem statement

Locally available resource analysis

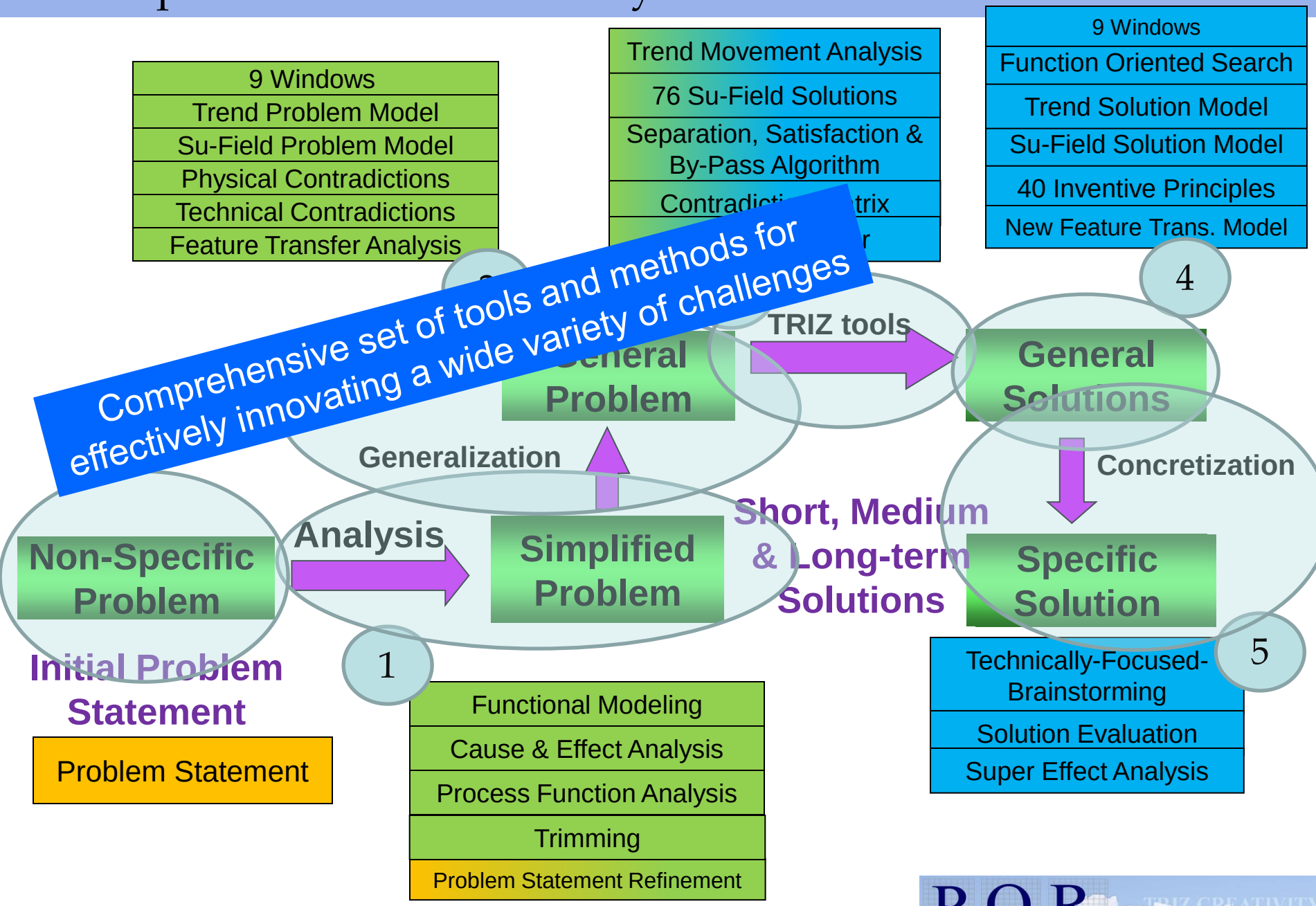
•The x factor allows the antibiotic to effect the bacteria but does not allow the efflux pump to remove the antibiotic:

•Shape of substrate
•Size of substrate
•Charge of substrate
•Binding mechanism of substrate
•Location of the substrate
•Shape of antibiotic
•Size of antibiotic
•Charge of antibiotic
•Binding mech …….

•The binding mechanism of the substrate allows the antibiotic to effect the bacteria but does not allow the efflux pump to remove the antibiotic



Back-Up - What are TRIZ and Systematic Innovation?



How are TRIZ/SI Used in the Pharmaceutical Industry?

- TRIZ/SI usage in the pharmaceutical industry covers a wide range of applications:

Analyzing and innovating specific equipment issues and problems

5. Pharmaceutical manufacturing process improvement

Operation	Function	Category	Type	Performance Level		Cost
				Parameter	Level	
Steel Fabrication	makes molten steel		P			4
Slab Forming	pour steel		T	location	excessive	2
	form steel		S	shape	sufficient	2
	cool steel		C	time	insufficient	3
	transport steel (from mold)		T	location	excessive	1
	create irregularities (on ingot surface)	H				
	polish slab		C	smoothness	sufficient	2
Transport	move slab		T	location	excessive	1
Fabricate Sheets	roll slab		P	thickness	excessive	3
	create micro-protrusion (edges and surfaces)	H				
	measure sheet		M	thickness	sufficient	1
	trim sheet		C	linearity	sufficient	2
Forming Pipes	cut sheet		P	length	sufficient	2
	die forms sheet		P	curvature	insufficient	2
	rollers form sheet		P	curvature	insufficient	2
Seaming	welds pipe		P		sufficient	4
Tempering	heats pipe		S	temperature	excessive	3
	cool steel		P	time	insufficient	3
Finishing	polishes pipe		C	smoothness	sufficient	3

Analyzing and innovating overall manufacturing process

How are TRIZ/SI Used in the Pharmaceutical Industry?

- TRIZ/SI usage in the pharmaceutical industry covers a wide range of applications:

Analyzing and innovating specific R&D and business process issues

Operation	Function	Category	Type	Performance Level		Cost
				Parameter	Level	
Steel Fabrication	makes molten steel		P			4
Slab Forming	pour steel		T	location	excessive	2
	form steel		S	shape	sufficient	2
	cool steel		C	time	insufficient	3
	transport steel (from mold)		T	location	excessive	1
	create irregularities (on ingot surface)	H				
	polish slab		C	smoothness	sufficient	2
Transport	move slab		T	location	excessive	1
Fabricate Sheets	roll slab		P	thickness	excessive	3
	create micro-protrusion (edges and surfaces)	H				
	measure sheet		M	thickness	sufficient	1
	trim sheet		C	linearity	sufficient	2
Forming Pipes	cut sheet		P	length	sufficient	2
	die forms sheet		P	curvature	insufficient	2
	rollers form sheet		P	curvature	insufficient	2
Seaming	welds pipe		P		sufficient	4
Tempering	heats pipe		S	temperature	excessive	3
	cool steel		P	time	insufficient	3
Finishing	polishes pipe		C	smoothness	sufficient	3

Analyzing and innovating overall R&D and business processes

6. Analysis and improvement of research and business process methodologies.

Which Pharma Companies Utilize TRIZ/SI?

Use of TRIZ is a closely guarded secret in may industries and particularly so in the pharmaceutical industry (however, below is a sampling of companies that are known to have used TRIZ):

P&G

Product and manufacturing innovation
Aspirin and Children's Nyquil innovations

Johnson & Johnson

Pharma development and advancement including:
oncology, immunology, neuroscience, infectious disease groups
Manufacturing process innovation

Bristol-Myers Squibb

MERCK

Macro product/market analysis and trending
Hep C product R&D

Lilly

Merger of TRIZ and Open Innovation -
Innovation Partnering Strategy

Pfizer

Injectable Bacitracin

gsk GlaxoSmithKline

Innovation in Sensodyne and Nicorette
Wide usage in vaccine development
R&D process development

Back-Up

Back-Up - What are TRIZ and Systematic Innovation?

- Systematic Innovation – Complete set of tool (includes TRIZ tools) that allow that application of innovation methodologies to a wide variety of industries and disciplines:

  - •Pharmaceutical
  - •Manufacturing
  - •Technology
  - •Computing
  - •Heath Care
  - •Product Development
  - •Services
  - •Banking/Finance

- Can be applied to any system (defined as a set of interacting components that create an output/function)

  - •Chemical Systems (e.g., pharma analysis/devel.)
  - •Research Systems (e.g., laboratory processes)
  - •Business Systems (e.g., compliance operations)
  - •Manufacturing Systems (e.g., drug manufacturing)
  - •Computing Systems (e.g., databases)
  - •Technical Systems (e.g., jet engines)
  - •Biological Systems (e.g., corn embryos)

Back-Up - What are TRIZ and Systematic Innovation?

What is the general process for solving problems?

Chemistry Example

What happens when fuel combusts?

Simplified

Methane reaction with oxygen

Abstraction

$CH_4 + 5O_2$

Reaction Formulation

$CO_2 + 2H_2O + 3O_2$

To Specific Solution

Carbon dioxide and water are released

How do we use TRIZ to solve problems?

Non-Specific Problem

Analysis

Simplified Problem

Higher level of abstraction

General Problem

TRIZ tools

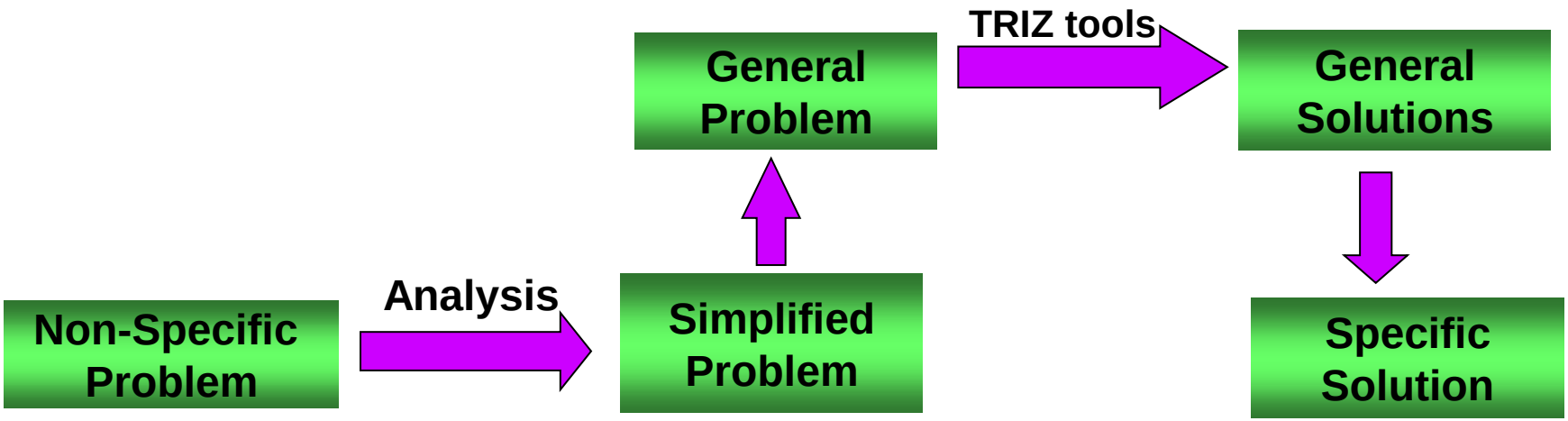
Solutions suggested on how similar problems resolved in other industries, sciences & technologies

General Solutions

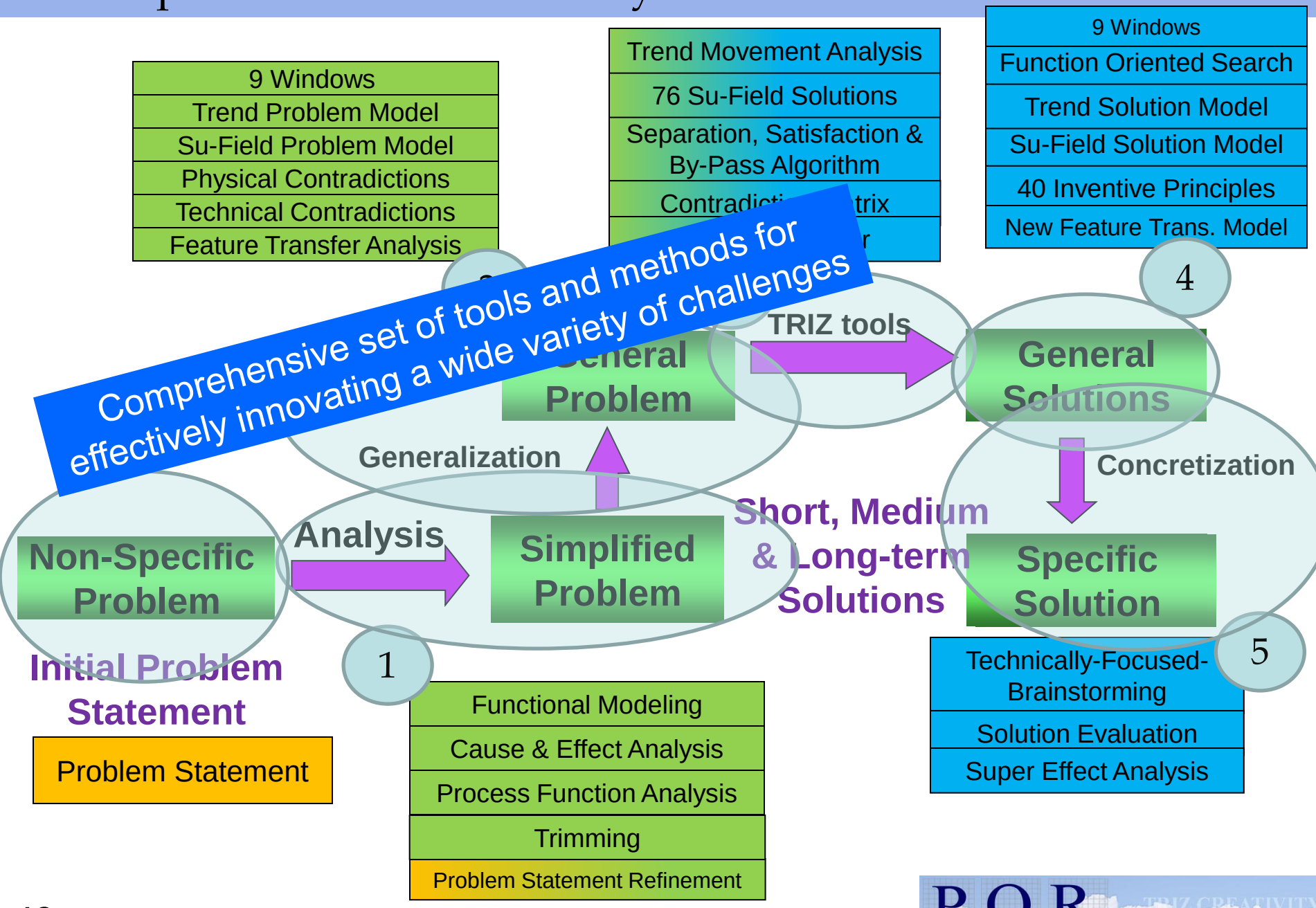
Focus creativity down multiple solution paths

Specific Solution

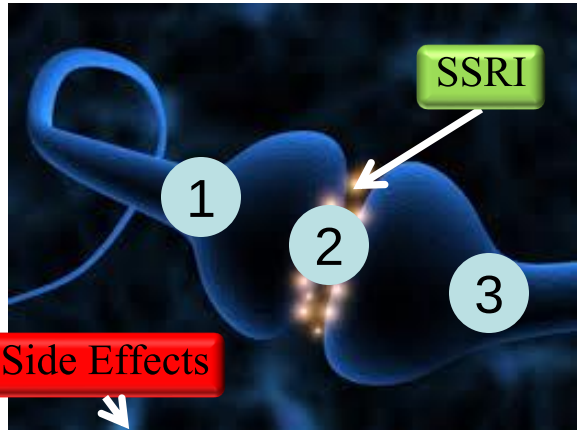
Back-Up - What are TRIZ and Systematic Innovation?



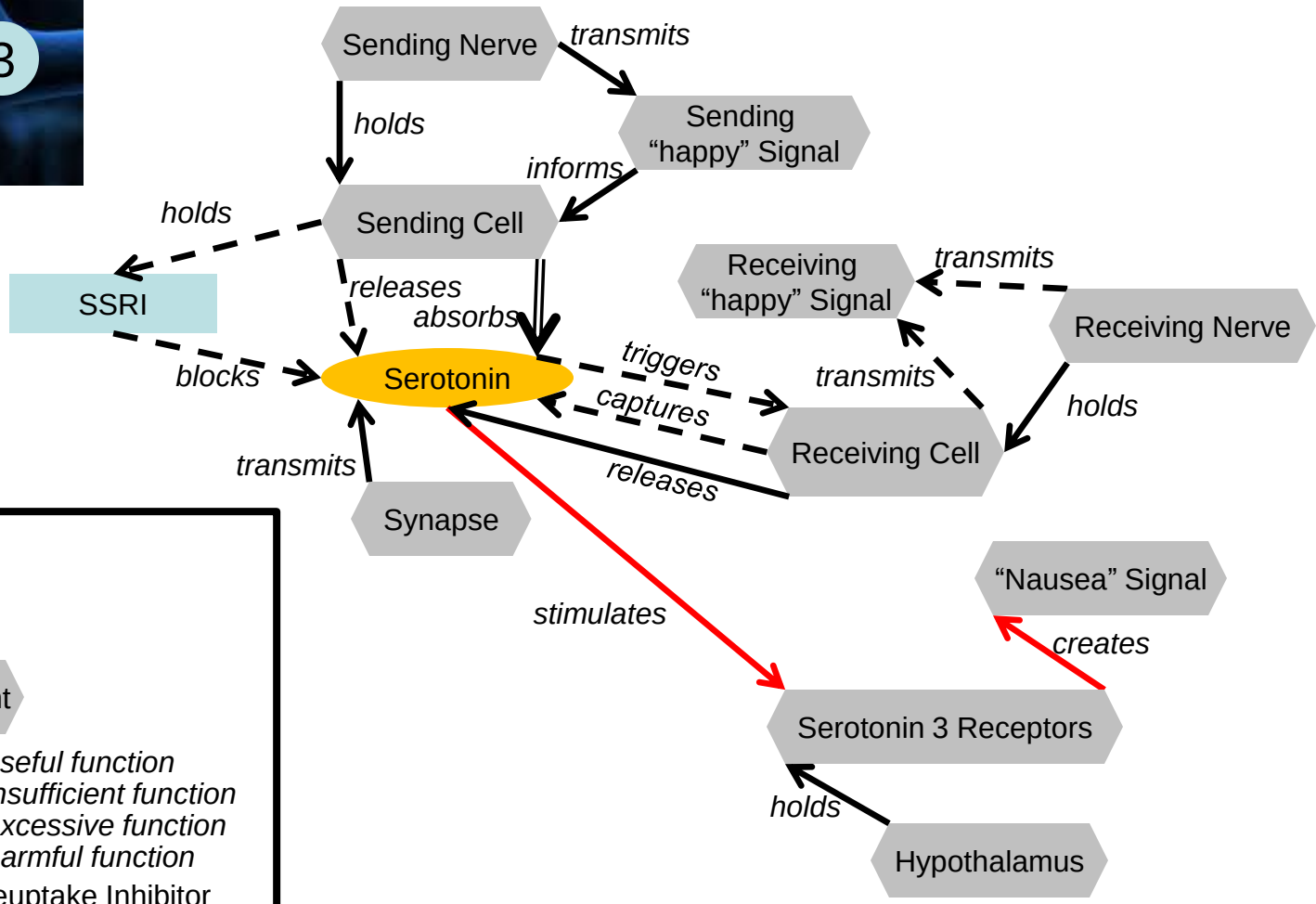
Back-Up - What are TRIZ and Systematic Innovation?

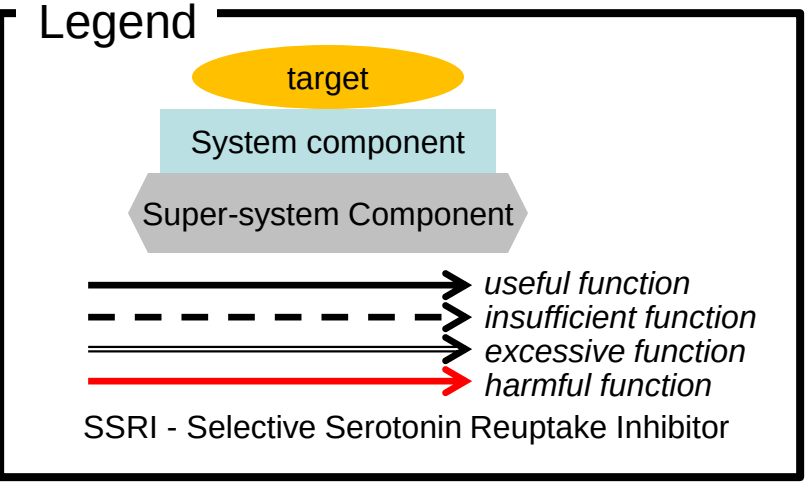


Innovation Case Study – *SSRIs Antidepressant*



•Innovation direction for improvement of SSRI antidepressant



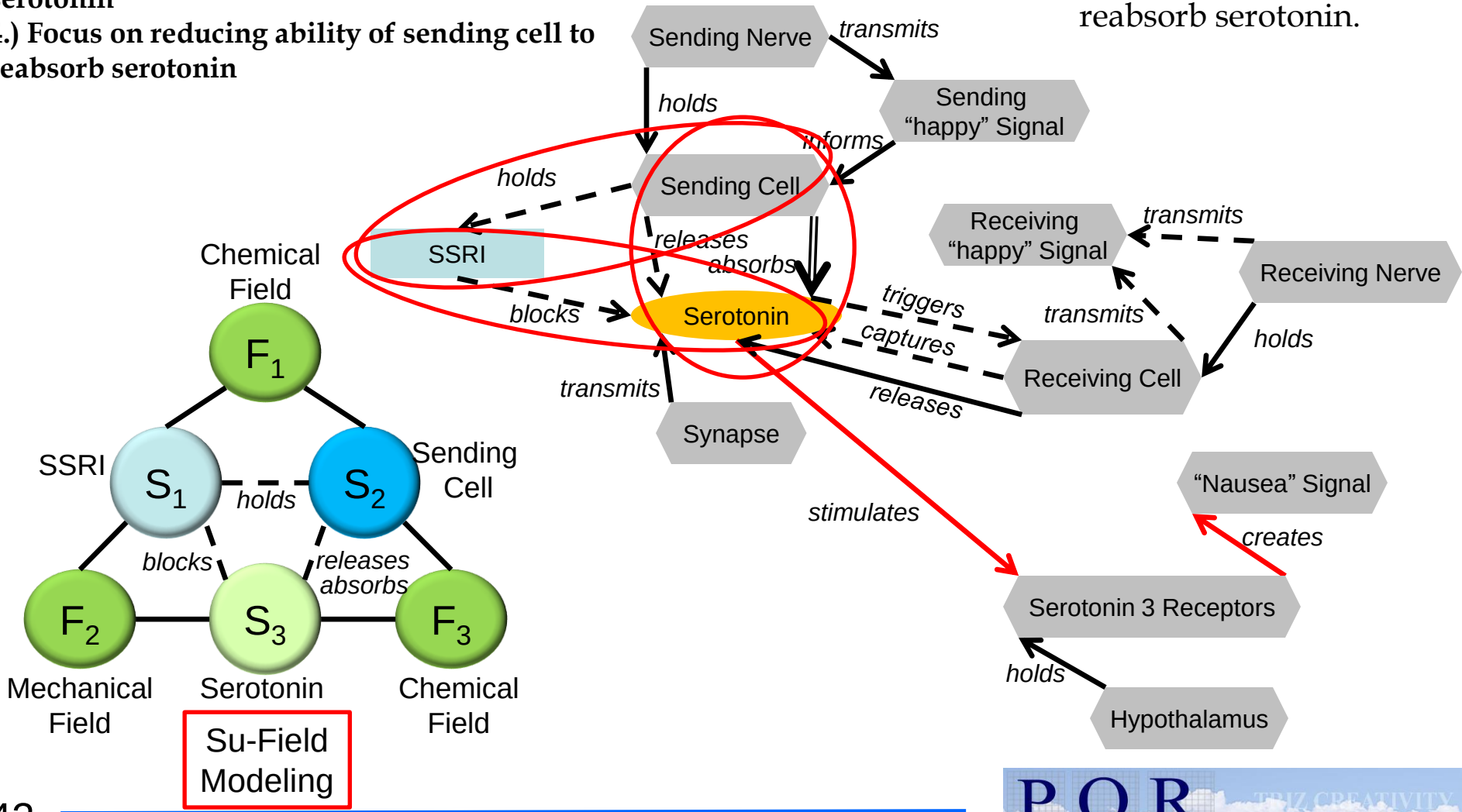


Innovation Case Study – *SSRIs Antidepressant*

•Innovation direction for improvement of SSRI antidepressant

1.) Focus on sending cells ability to hold SSRI
2.) Focus on ability of SSRI to block serotonin
3.) Focus on ability of sending cell to release serotonin
4.) Focus on reducing ability of sending cell to reabsorb serotonin

Advancements focusing on ability of SSRI to reduce sending cells ability to reabsorb serotonin.

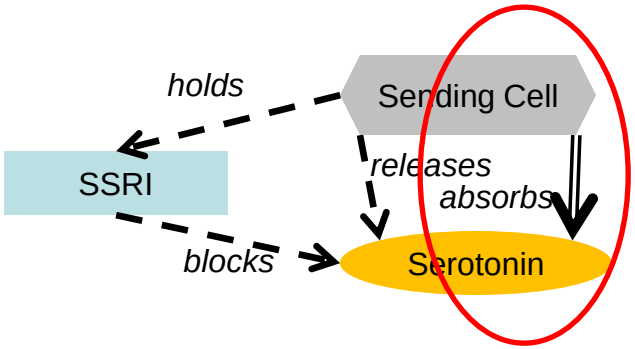


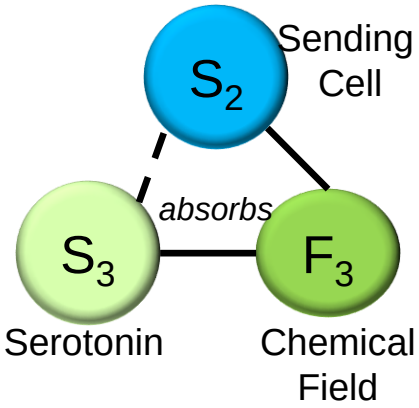
Innovation Case Study – *SSRIs Antidepressant*

•Innovation direction for improvement of SSRI antidepressant

Advancements focusing on ability of SSRI to reduce sending cells ability to reabsorb serotonin.

4.) Focus on reducing ability of sending cell to reabsorb serotonin





Once Functions are Understood TRIZ Suggests Innovation Pathways

Multiple Su-fields

- Chain Su-Field Model
- Double Su-Field Model

Enforcing Su-Field Models

Applying More Controllable Fields

- Applying More Controllable Fields
- Fragmentation of S_2
- Applying Capillary and Porous Substances
- Dynamization
- Structuring Fields
- Structuring Substances

Enforcing by Matching Rhythms

- Matching Rhythms of F and S_1 or S_2
- Matching Rhythms of F_1 and F_2
- Matching Incompatible or Previously Independent Actions

Use EM Fields/Substances

- Pre-Ferro-Field Models
- Ferro-Field Models
- Electro-Magnetic Liquids
- Applying Capillary Structures in Ferro-Field Models
- Complex Ferro-Field Models
- Ferro-Field Models with the Environment
- Applying Physical Effects and Phenomena
- Dynamization
- Structuring
- Matching Rhythms in Ferro-Field Models
- Electro-Field Models
- Rheological Liquids

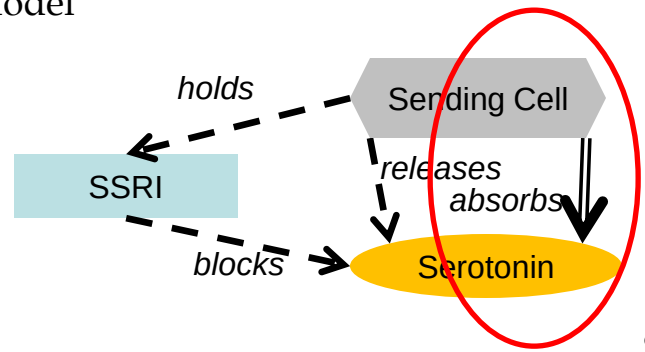
Innovation Case Study – *SSRIs Antidepressant*

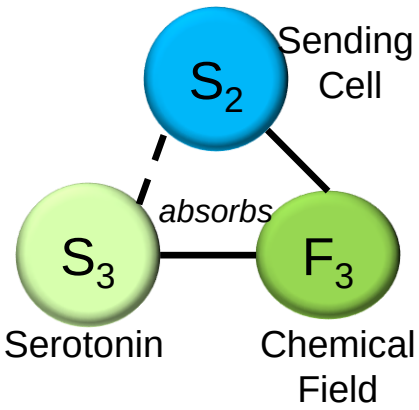
•Innovation direction for improvement of SSRI antidepressant

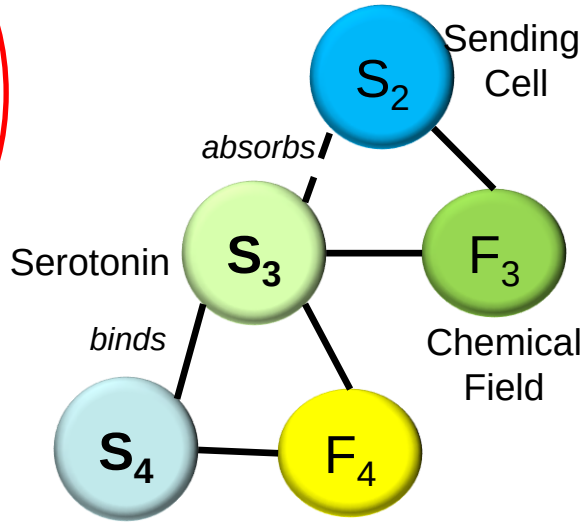
Advancements focusing on ability of SSRI to reduce sending cells ability to reabsorb serotonin.

Multiple Su-fields

- Chain Su-Field Model
- Double Su-Field Model







Add a second substance (S_4) that inhibits the functioning of the serotonin transport protein.

Innovation Case Study – *SSRIs Antidepressant*

•Innovation direction for improvement of SSRI antidepressant

6 Formulation Investigation Options:

1.) add a substance that binds with the transporter protein's sodium ion's binding site

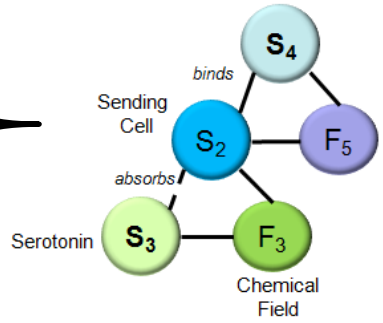
2.) add a substance that binds with transporter protein's chloride ion's binding site

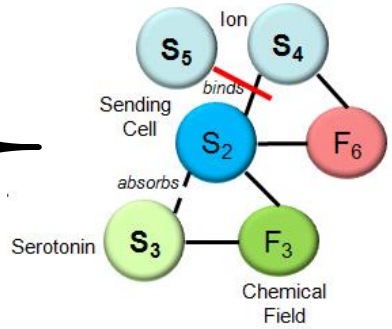
3.) add a substance that binds with transporter protein's serotonin's bind site

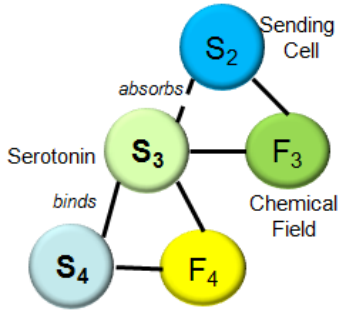
4.) add a substance that binds with the sodium ion and prevents it from binding with the transporter protein

5.) add a substance that binds with the chloride ion and prevents it from binding with the transporter protein

6.) add a substance that binds with the serotonin and prevents it from binding with the transporter protein







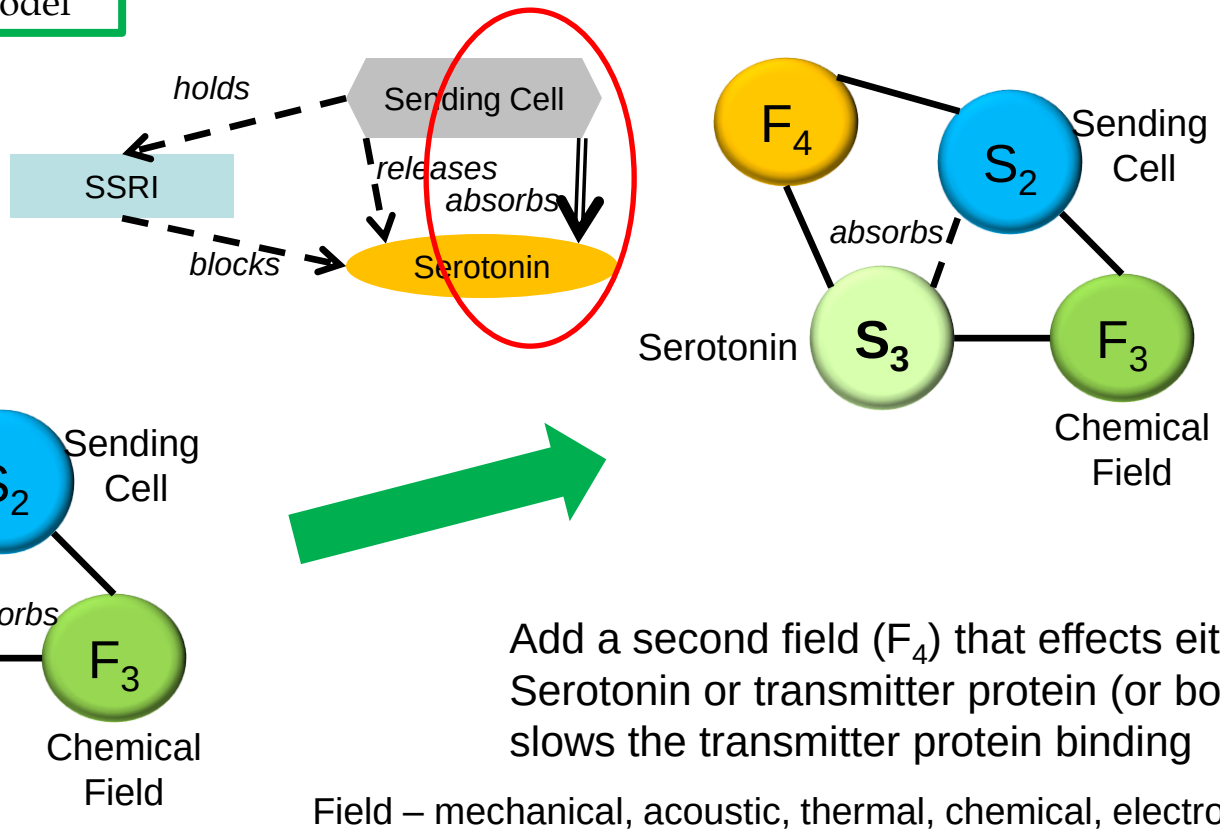
Innovation Case Study – *SSRIs Antidepressant*

•Innovation direction for improvement of SSRI antidepressant

Advancements focusing on ability of SSRI to reduce sending cells ability to reabsorb serotonin.

Multiple Su-fields

- Chain Su-Field Model
- Double Su-Field Model



Add a second field (F_4) that effects either Serotonin or transmitter protein (or both) and slows the transmitter protein binding

Field – mechanical, acoustic, thermal, chemical, electro-magnetic

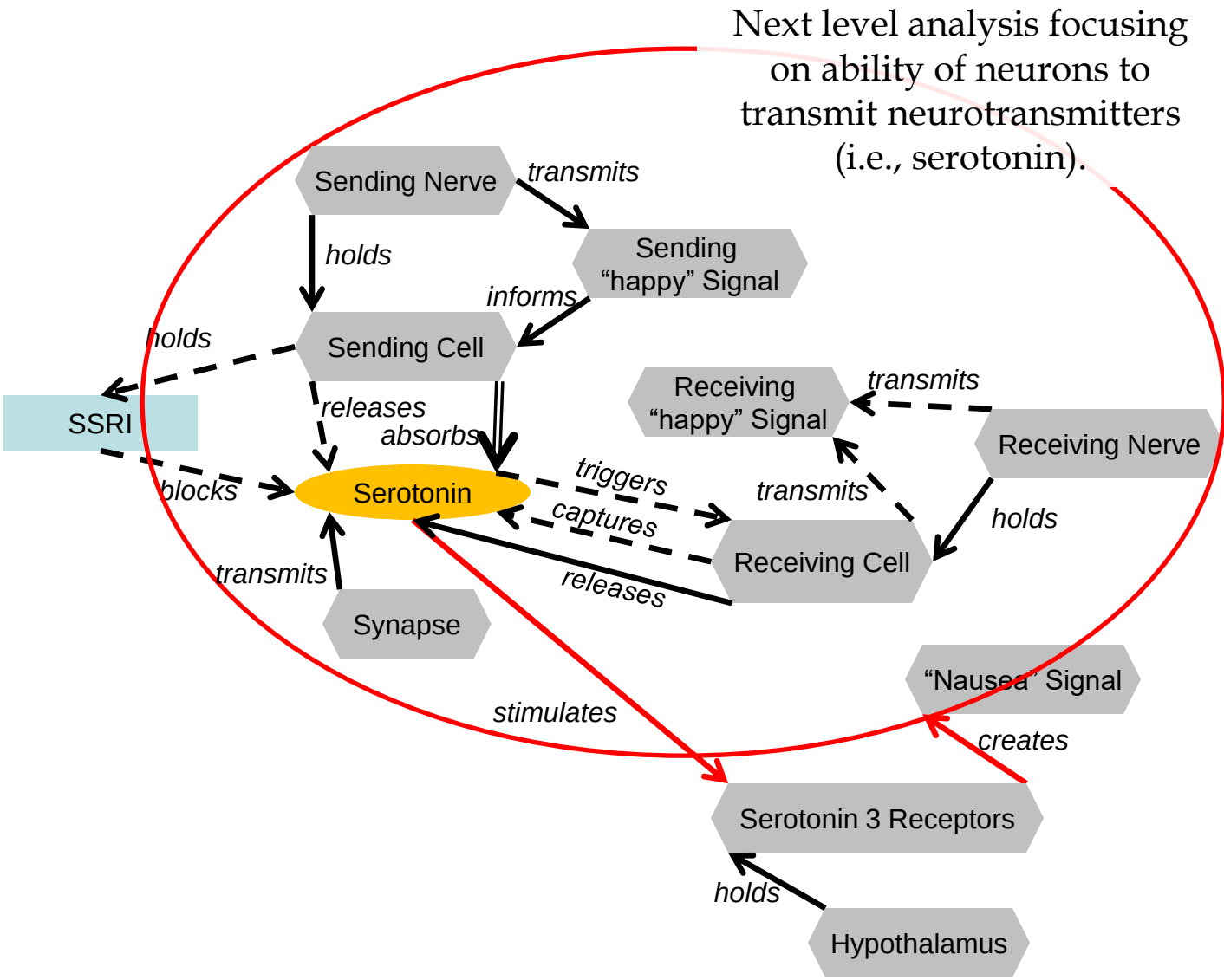
Repeat solution conceptualization utilizing remaining Inventive Solutions

Multiple Su-fields

- Chain Su-Field Model
- Double Su-Field Model

Innovation Case Study – *Neurotransmitter Drilldown*

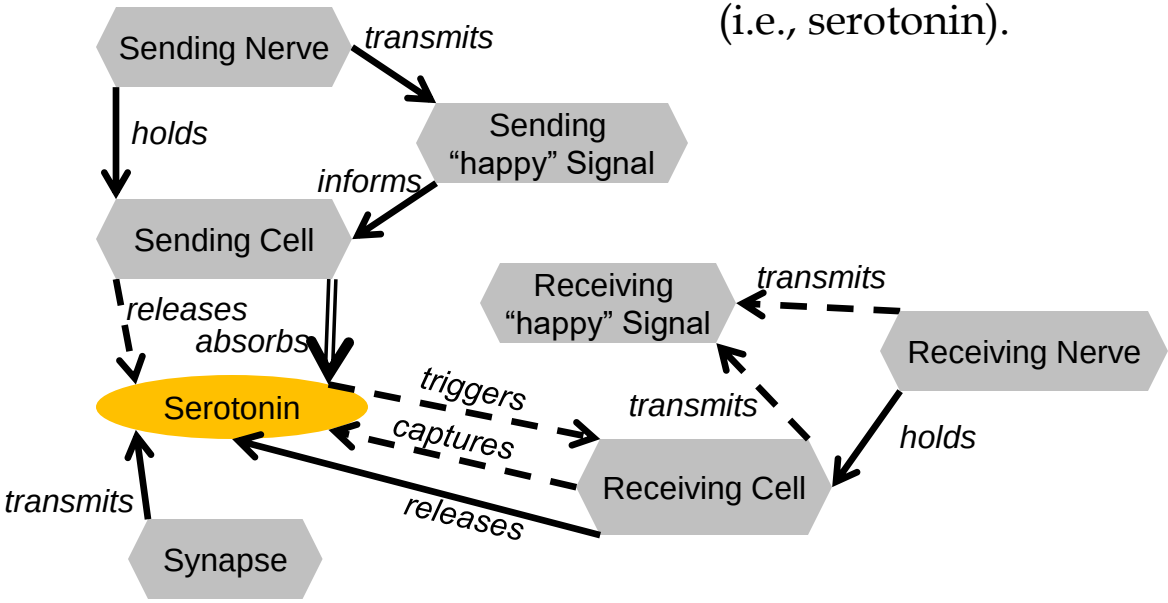
•Innovation direction drill down for neurotransmitter functioning



Innovation Case Study – *Neurotransmitter Drilldown*

•Innovation direction drill down for neurotransmitter functioning

Next level analysis focusing on ability of neurons to transmit neurotransmitters (i.e., serotonin).



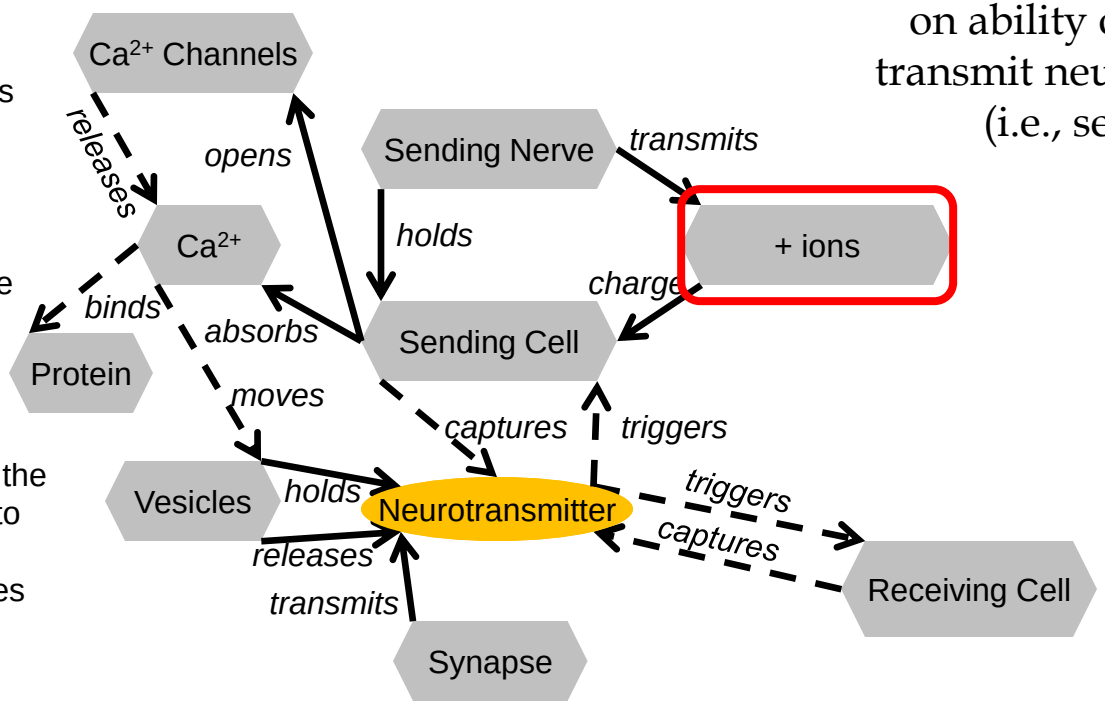
Requires a deeper analysis of how neurons work.

Innovation Case Study – *Neurotransmitter Drilldown*

1.) The action potential signal arrives at the axon terminal.
2.) The local depolarization causes Ca^{2+} channels to open.
3.) Ca^{2+} enters the presynaptic cell because its concentration is greater outside the cell than inside.
4.) The Ca^{2+}, by binding with proteins, causes vesicles filled with neurotransmitter to migrate towards the presynaptic membrane.
5.) The presynaptic membrane and vesicle now forms a continuous membrane, so that the neurotransmitter is released into the synaptic cleft.
6.) The neurotransmitter diffuses through the synaptic cleft and binds with receptor channel membranes that are located in both presynaptic and postsynaptic membranes.

•Innovation direction drill down for neurotransmitter functioning

Next level analysis focusing on ability of neurons to transmit neurotransmitters (i.e., serotonin).

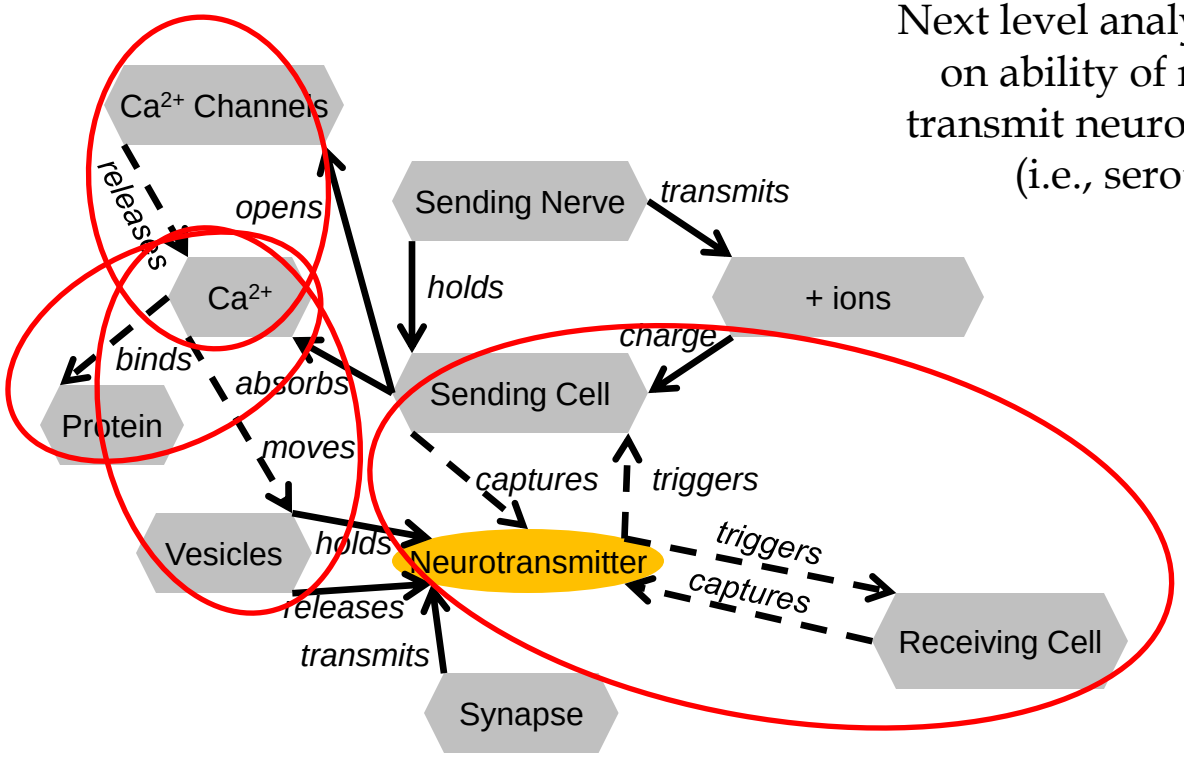


Requires a deeper analysis of how neurons work.

Innovation Case Study – *Neurotransmitter Drilldown*

•Innovation direction drill down for neurotransmitter functioning

Next level analysis focusing on ability of neurons to transmit neurotransmitters (i.e., serotonin).



Now innovation analysis can be focused on a lower level of neuron function:

1.) how to improve release of Ca^{2+}

2.) how to improve Ca^{2+} and protein binding

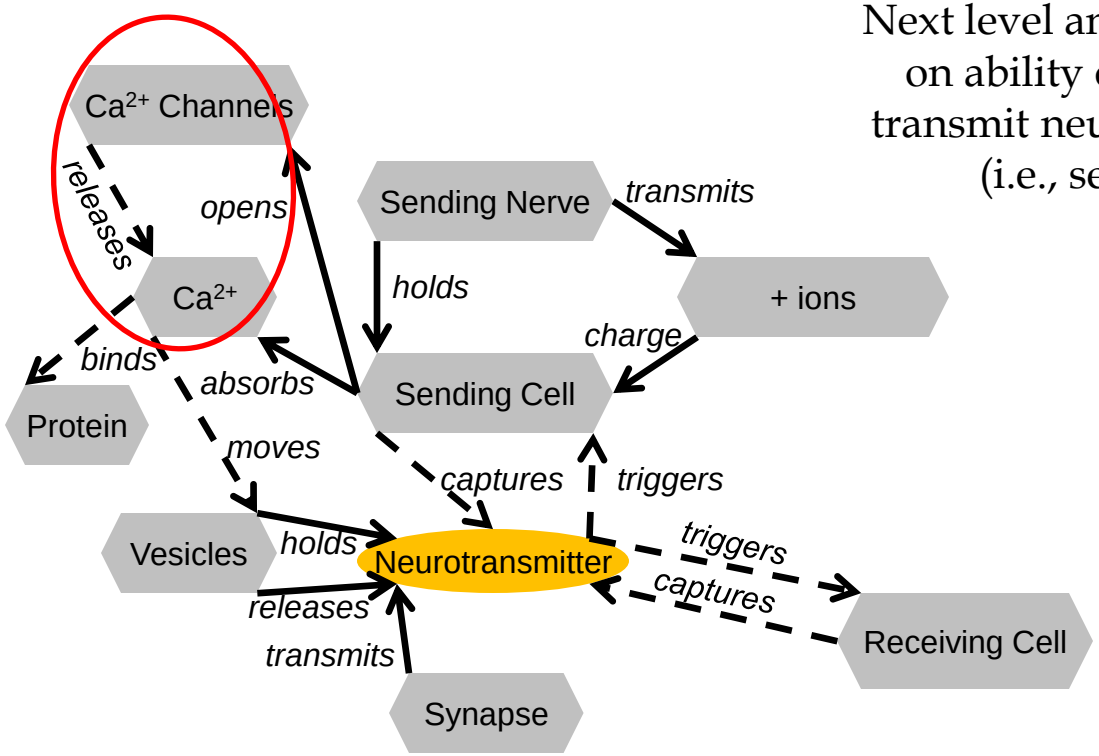
3.) how to improve movement of vesicles to membrane wall

4.) how to improve interaction of neurotransmitter

Innovation Case Study – *Neurotransmitter Drilldown*

•Innovation direction drill down for neurotransmitter functioning

Next level analysis focusing on ability of neurons to transmit neurotransmitters (i.e., serotonin).



Now innovation analysis can be focused on a lower level of neuron function:

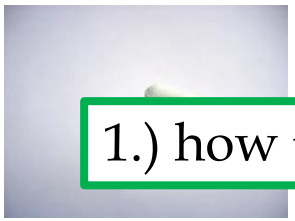
1.) how to improve release of Ca^{2+}

- TRIZ/SI usage in the pharmaceutical industry covers a wide range of applications:

3. Trending analysis of treatment delivery options
4. Packaging (delivery mode) innovation

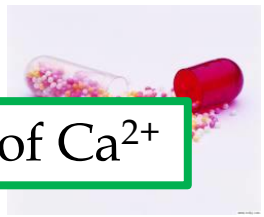
Example – Drug dynamization and packaging trending

1.) how to improve release of Ca^{2+}



monolith

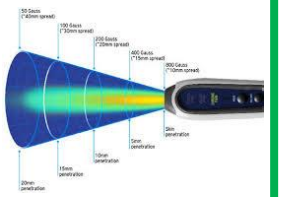
shifted parameter monolith



segmented

liquid

gas

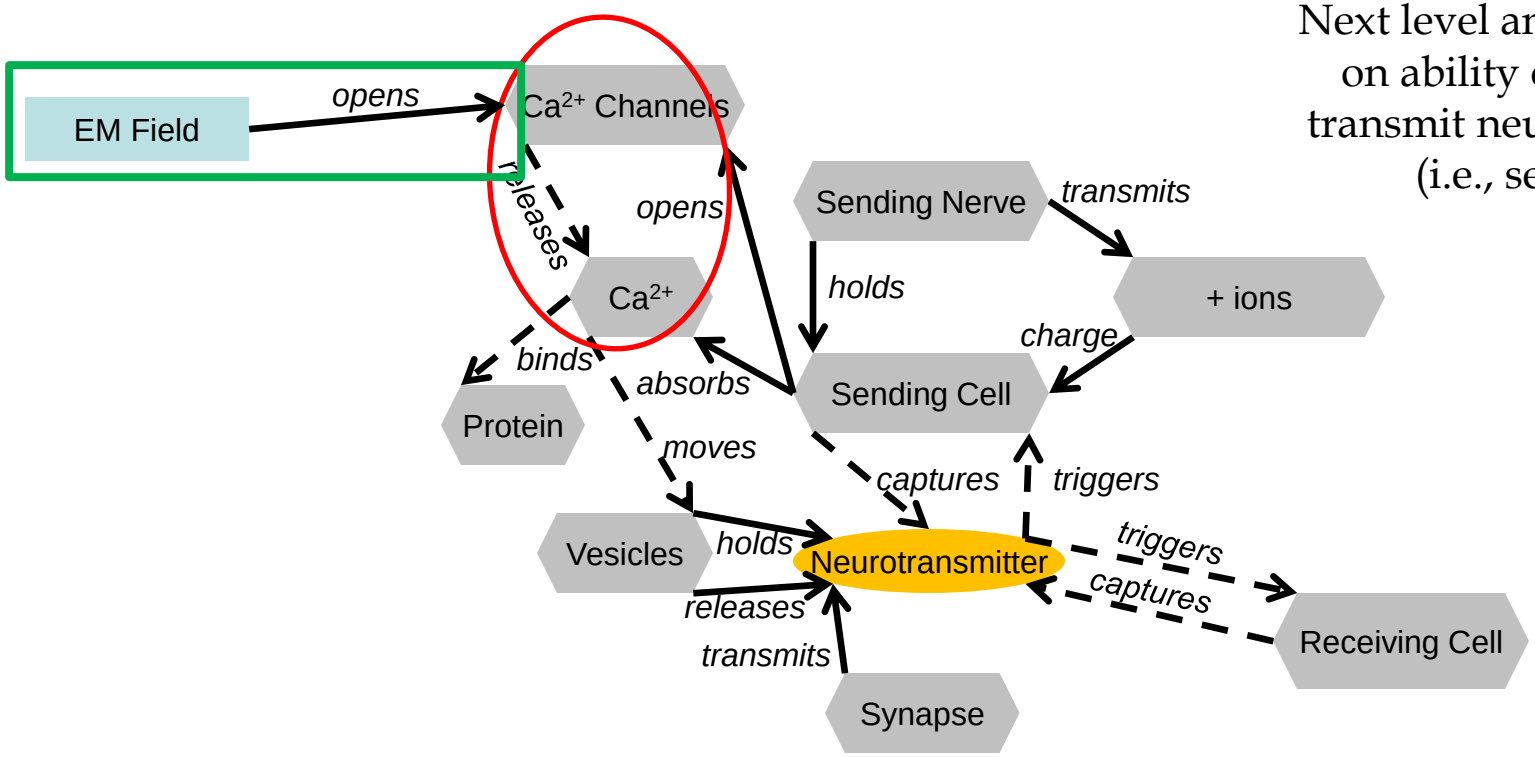


field

Innovation Case Study – *Neurotransmitter Drilldown*

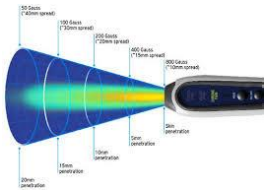
•Innovation direction drill down for neurotransmitter functioning

Next level analysis focusing on ability of neurons to transmit neurotransmitters (i.e., serotonin).



Now innovation analysis can be focused on a lower level of neuron function:

1.) how to improve release of Ca^{2+}



field