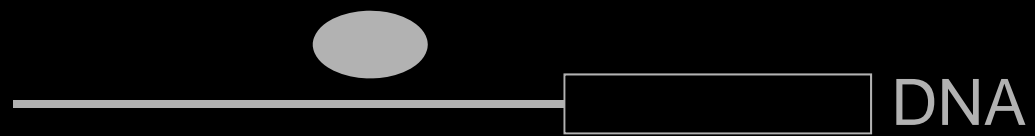


Social regulation of gene expression

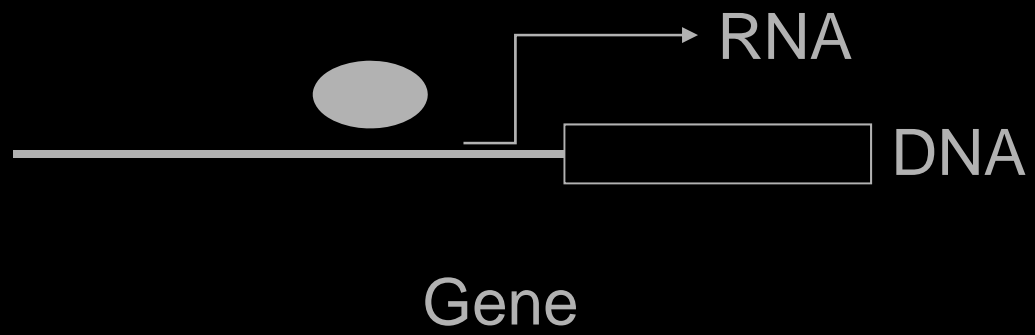
Steve W. Cole, Ph.D.
UCLA School of Medicine
Division of Hematology-Oncology

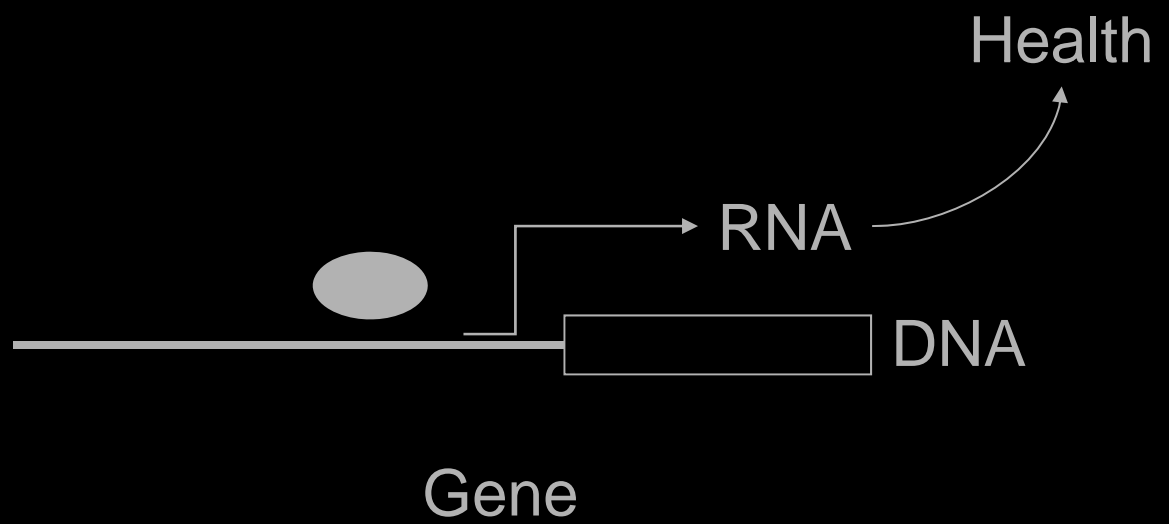


Gene



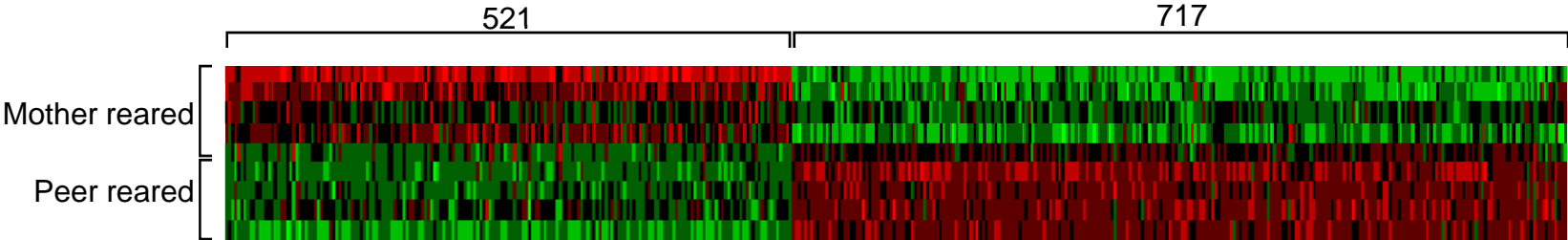
Gene

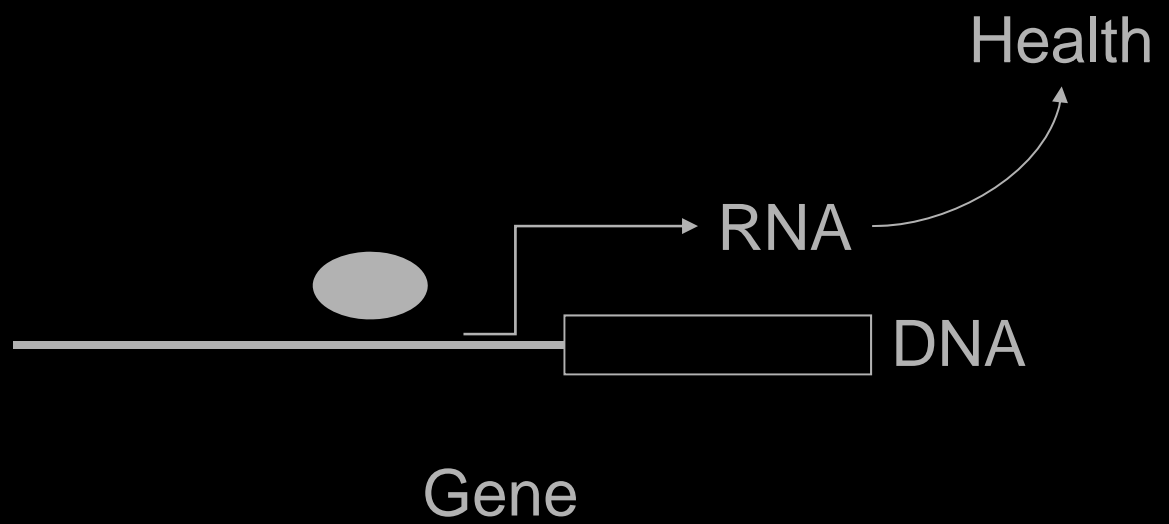


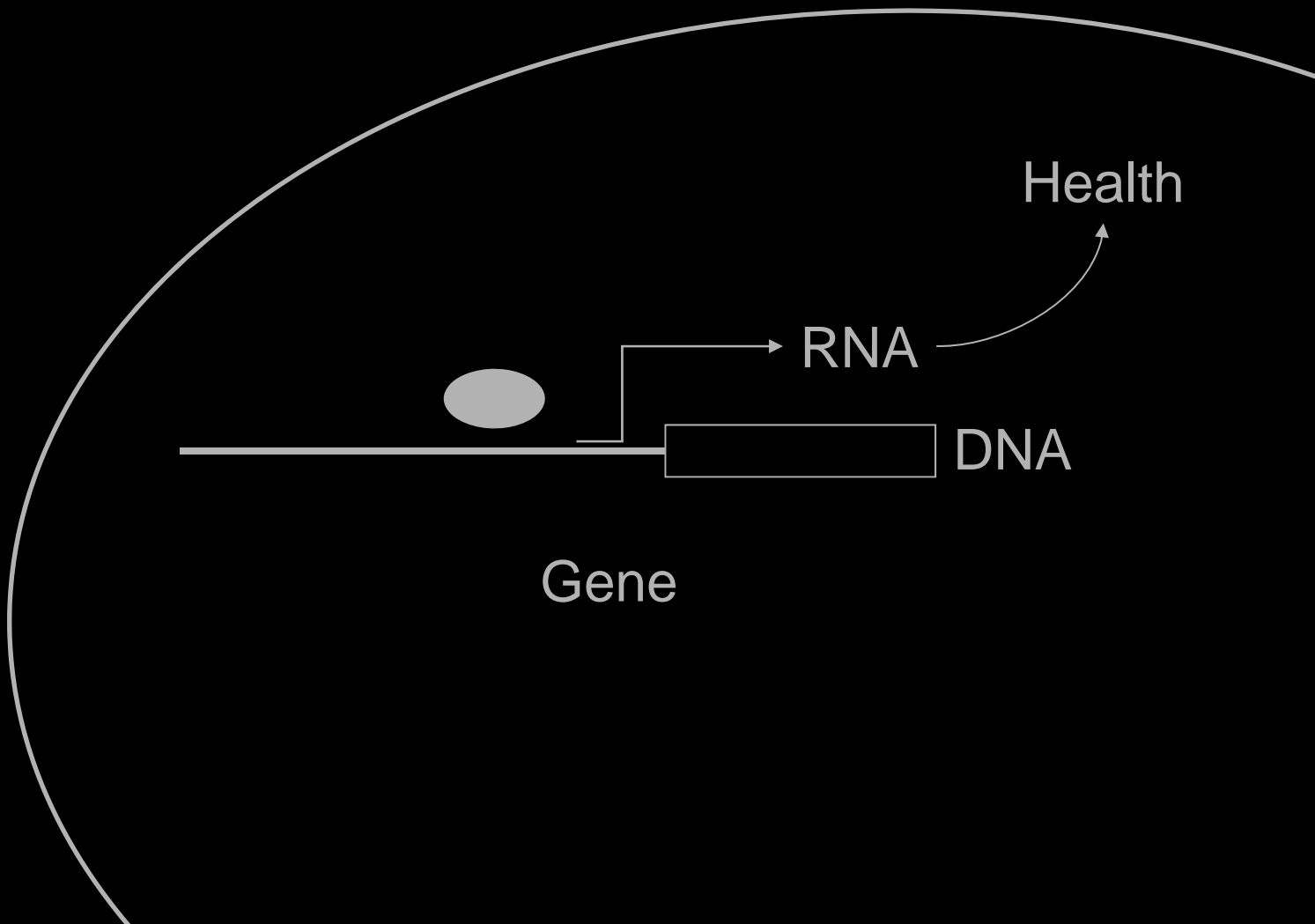


Early life social conditions

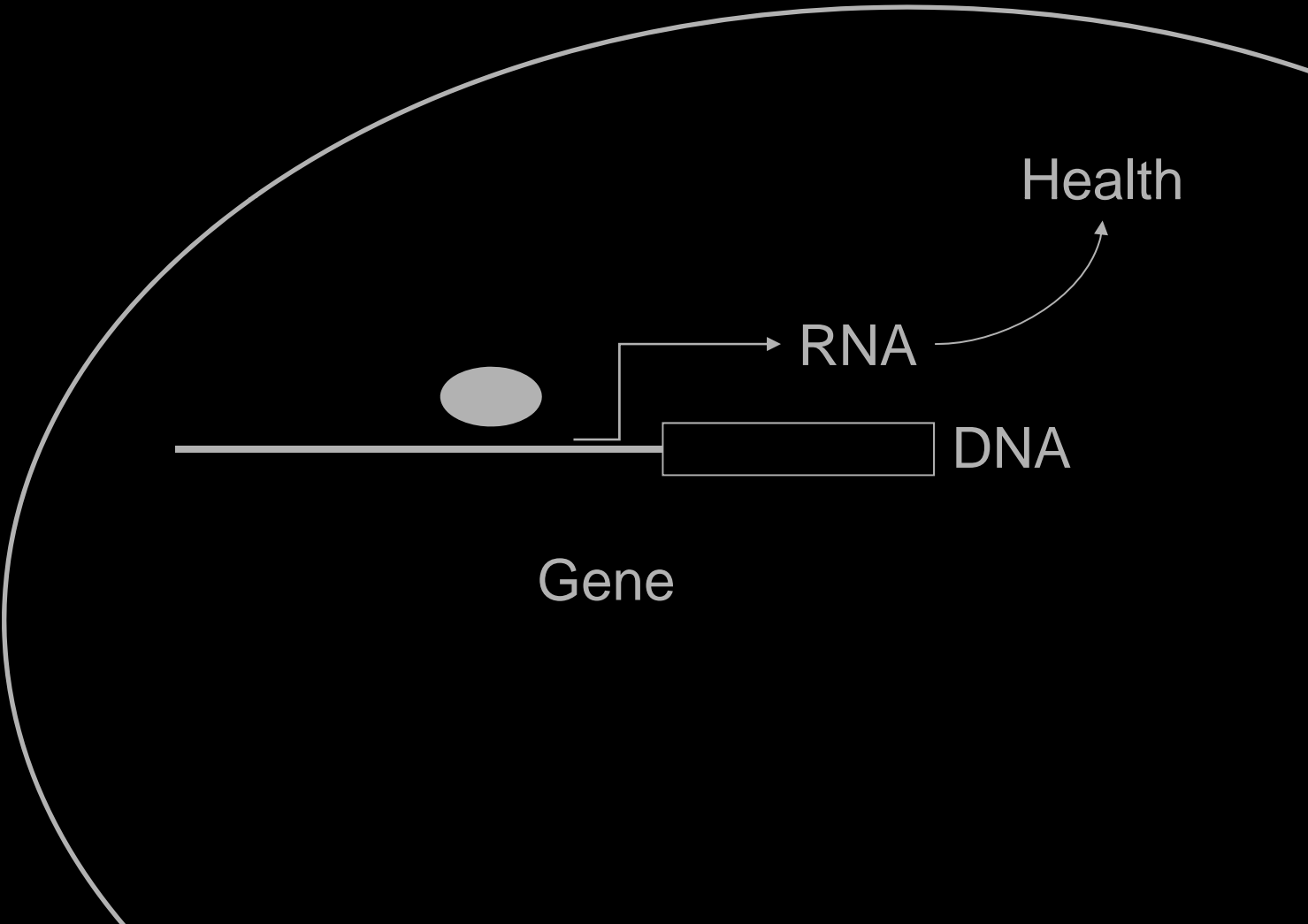
S. Suomi







Social Environment



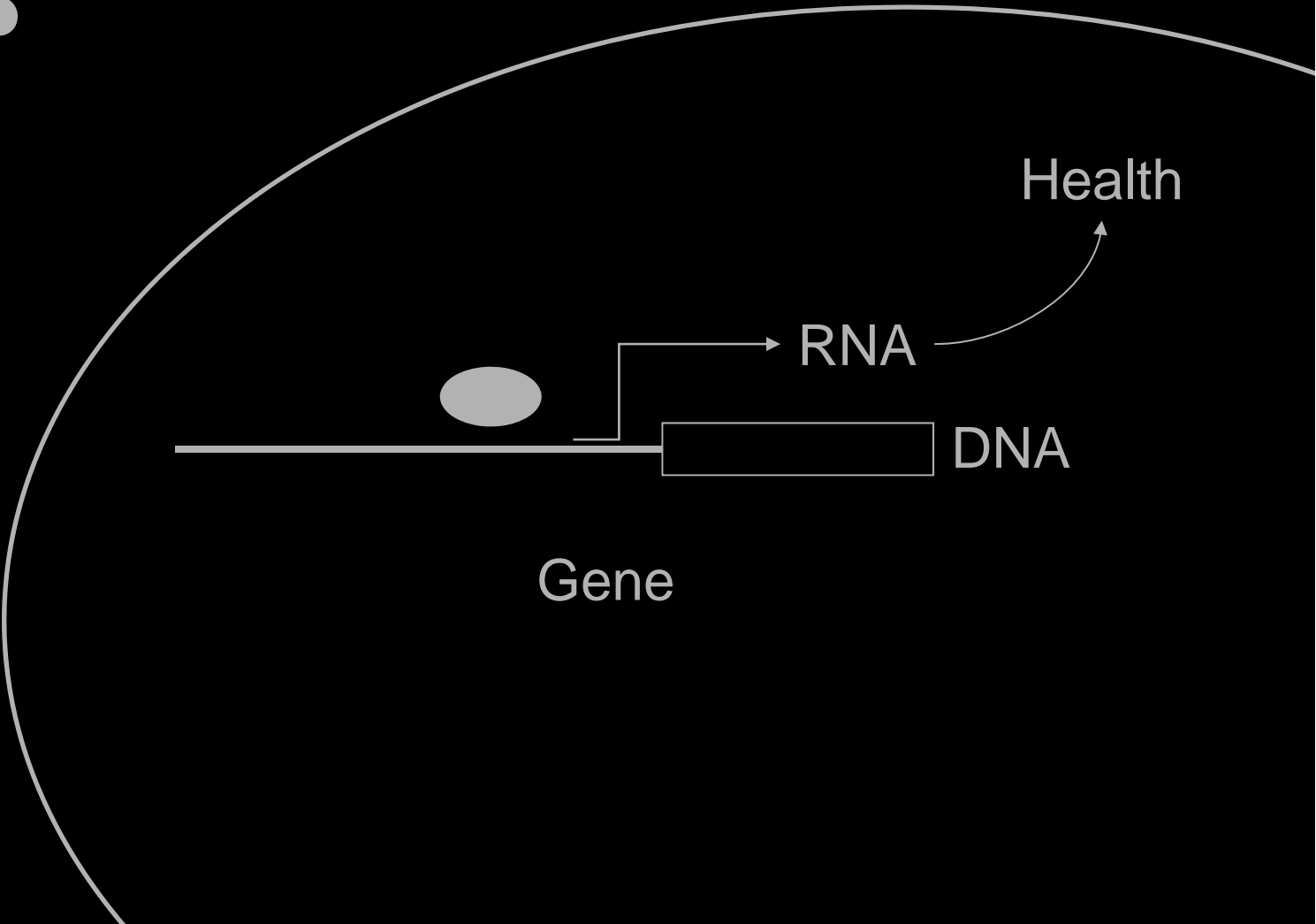
Health

RNA

DNA

Gene

Social Environment



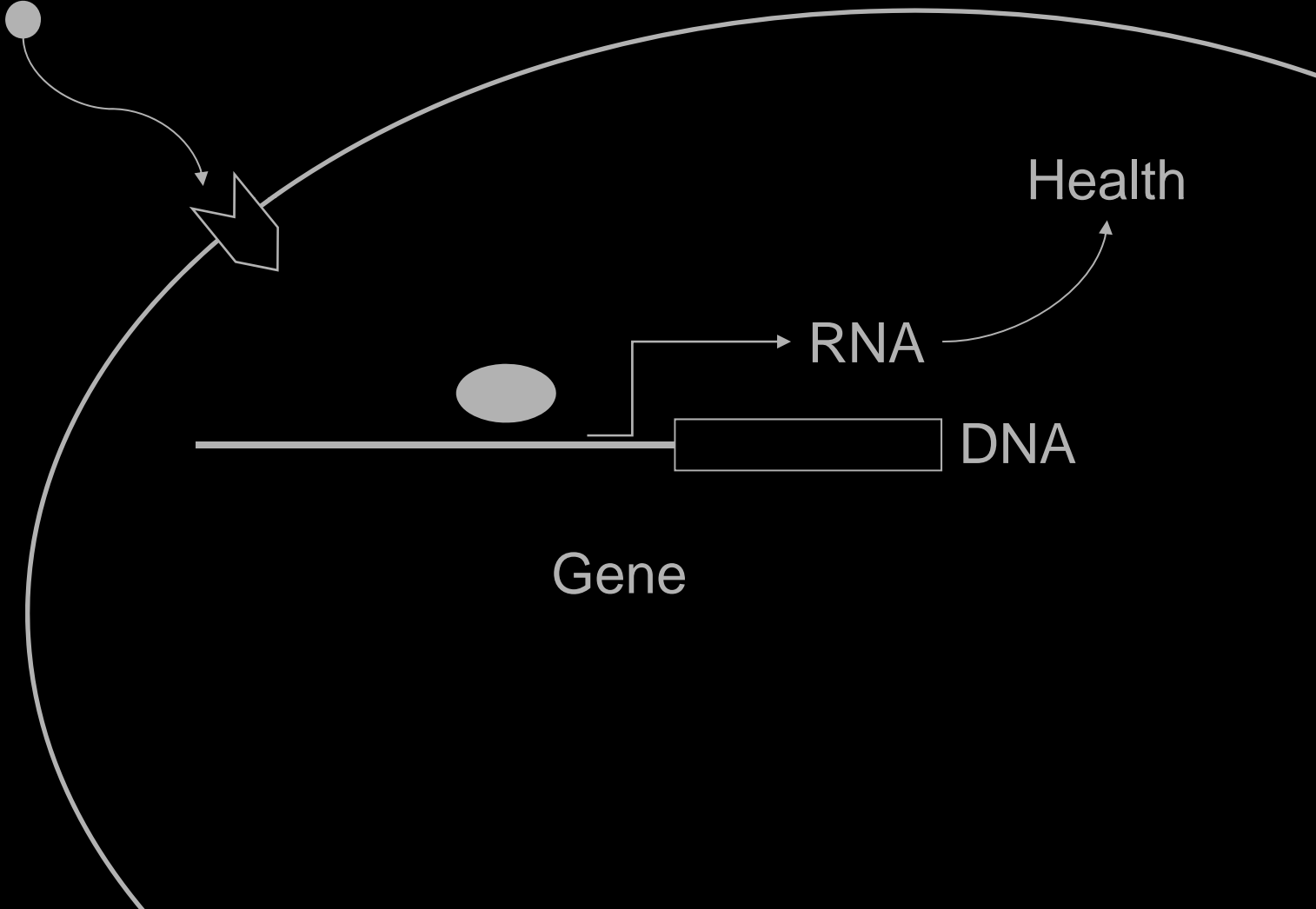
Health

RNA

DNA

Gene

Social Environment



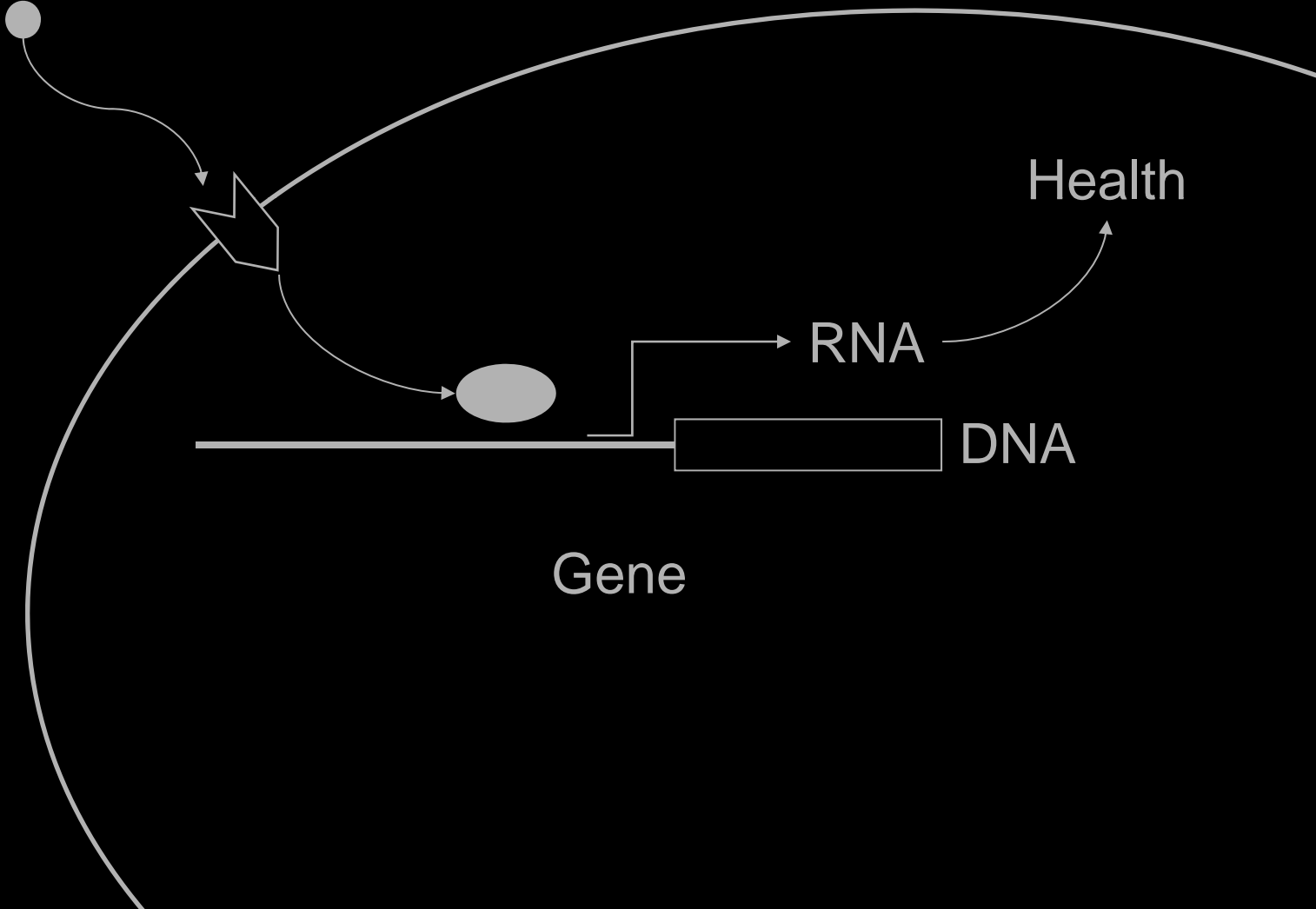
Health

RNA

DNA

Gene

Social Environment



Health

RNA

DNA

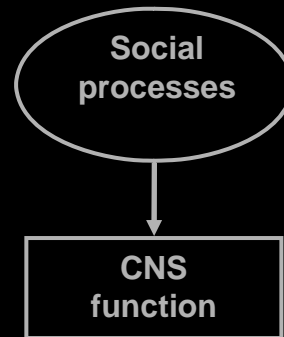
Gene

Social signal transduction

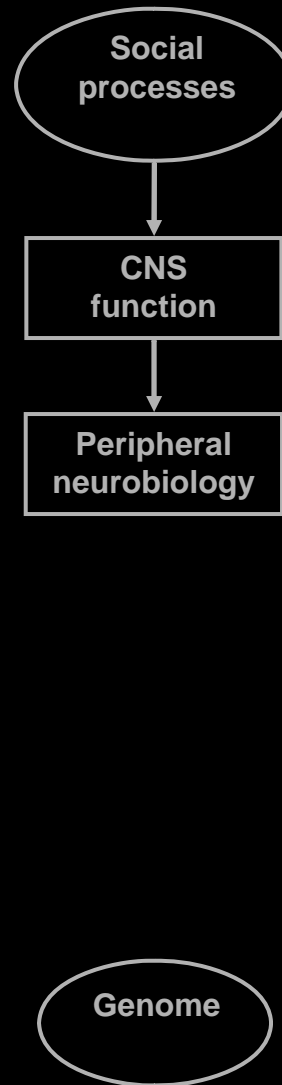
Social
processes

Genome

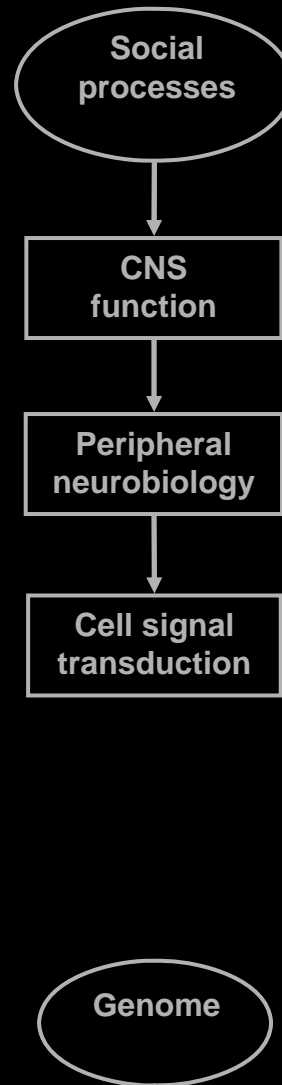
Social signal transduction



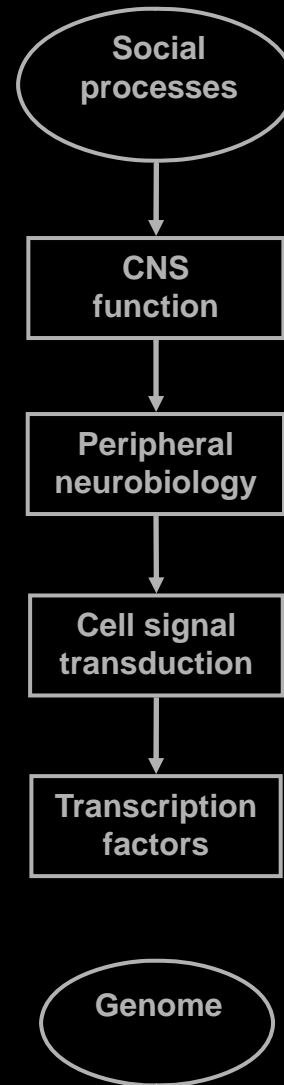
Social signal transduction



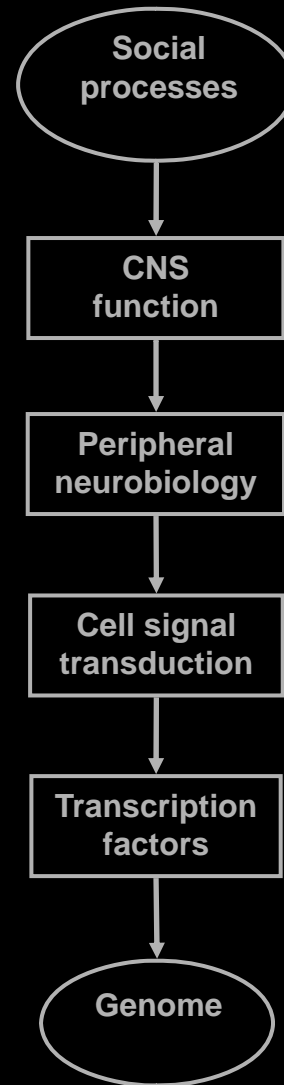
Social signal transduction



Social signal transduction

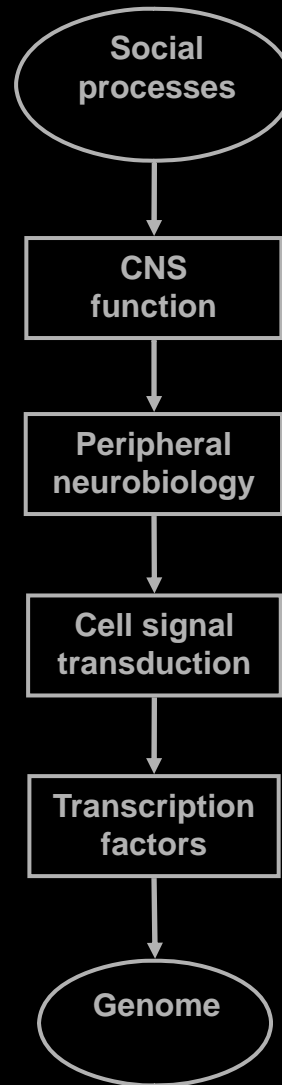


Social signal transduction



Social signal transduction

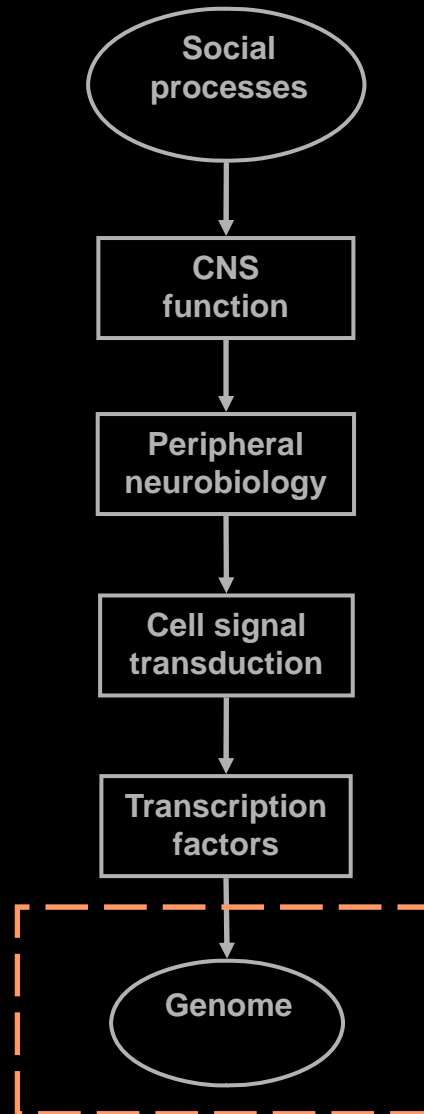
Simple questions



Social signal transduction

Simple questions

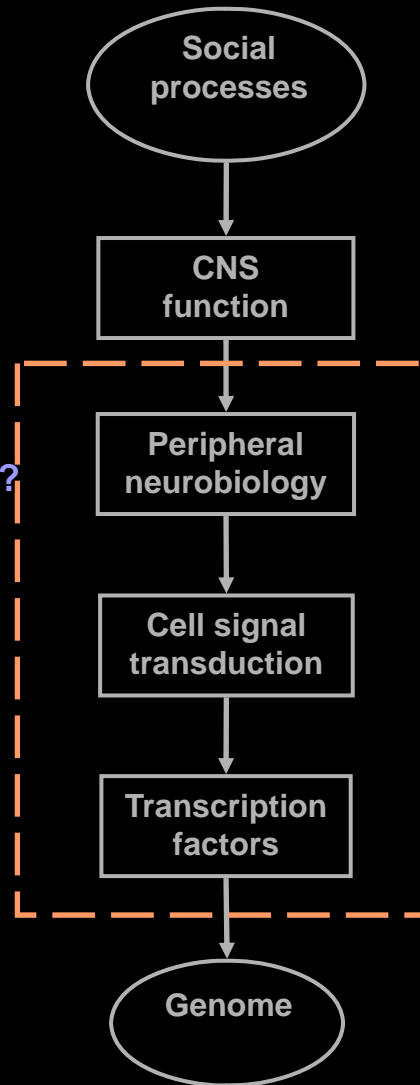
1. Which gene modules are sensitive to social processes?



Social signal transduction

Simple questions

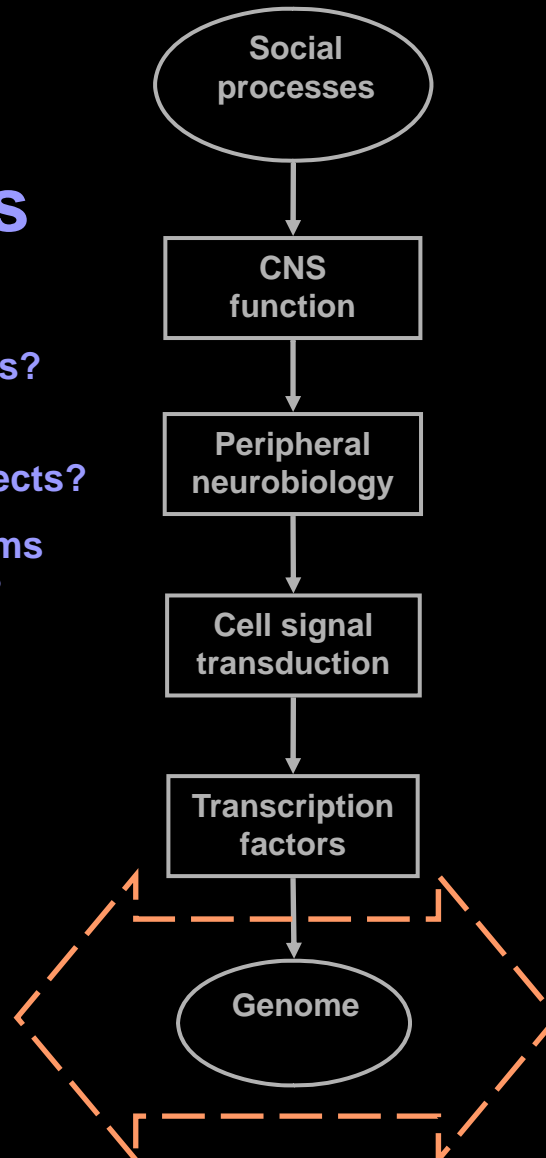
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?



Social signal transduction

Simple questions

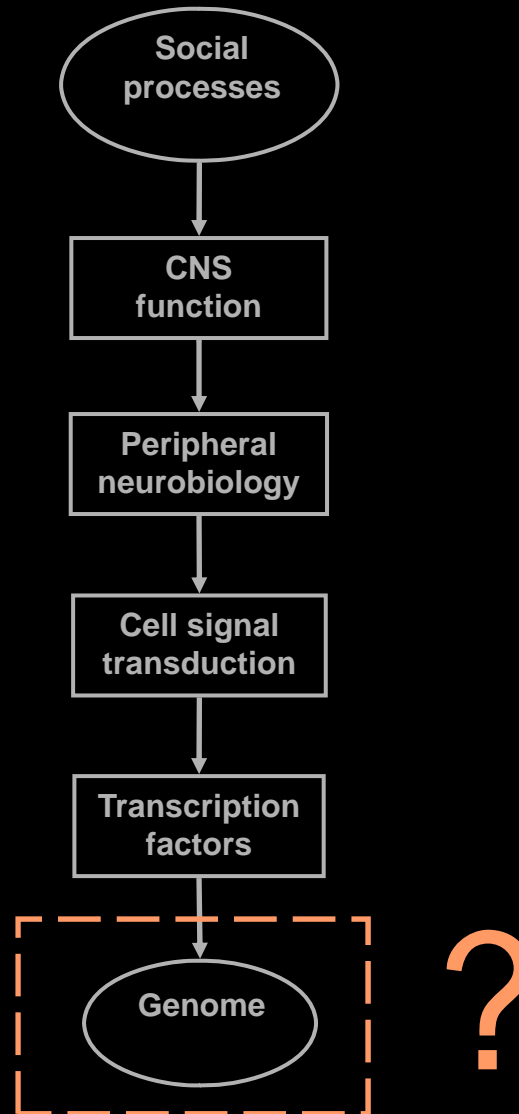
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?
3. Which genetic polymorphisms modulate social influences?



Social signal transduction

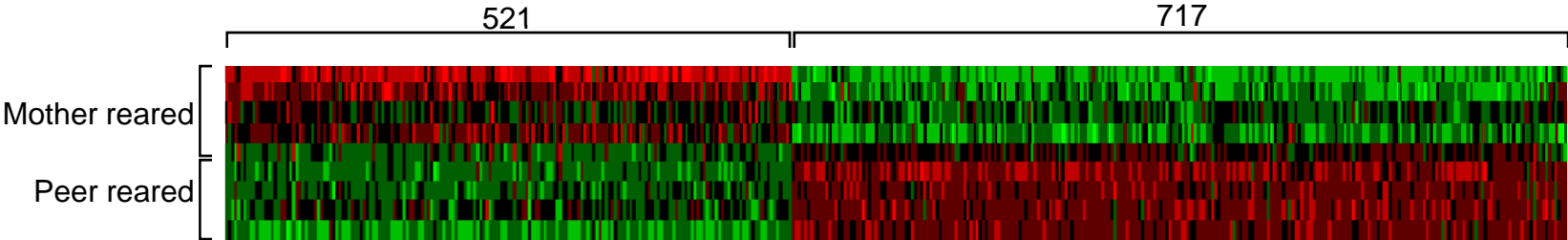
Simple questions

1. Which gene modules are sensitive to social processes?
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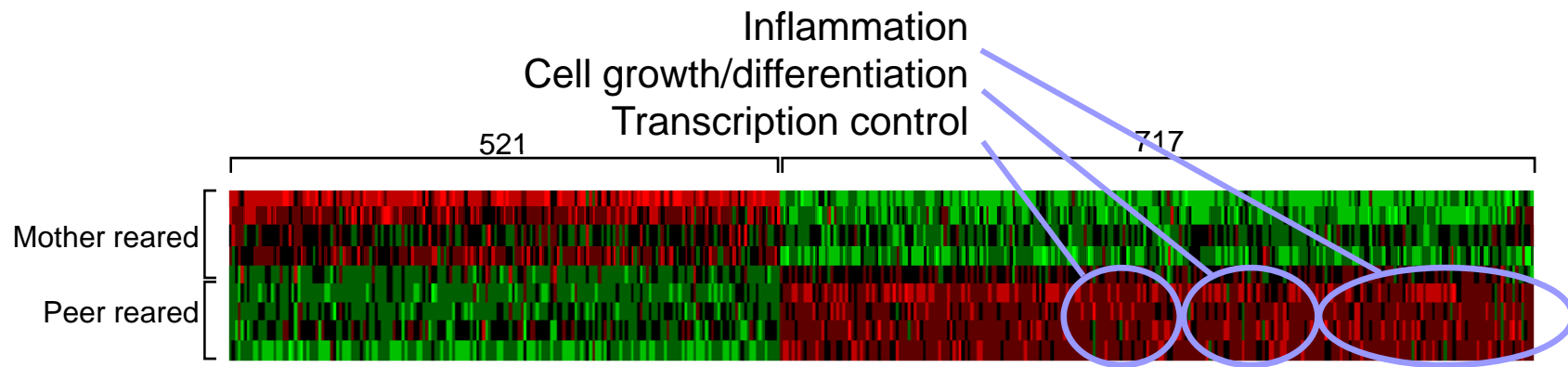
Early life social conditions

S. Suomi



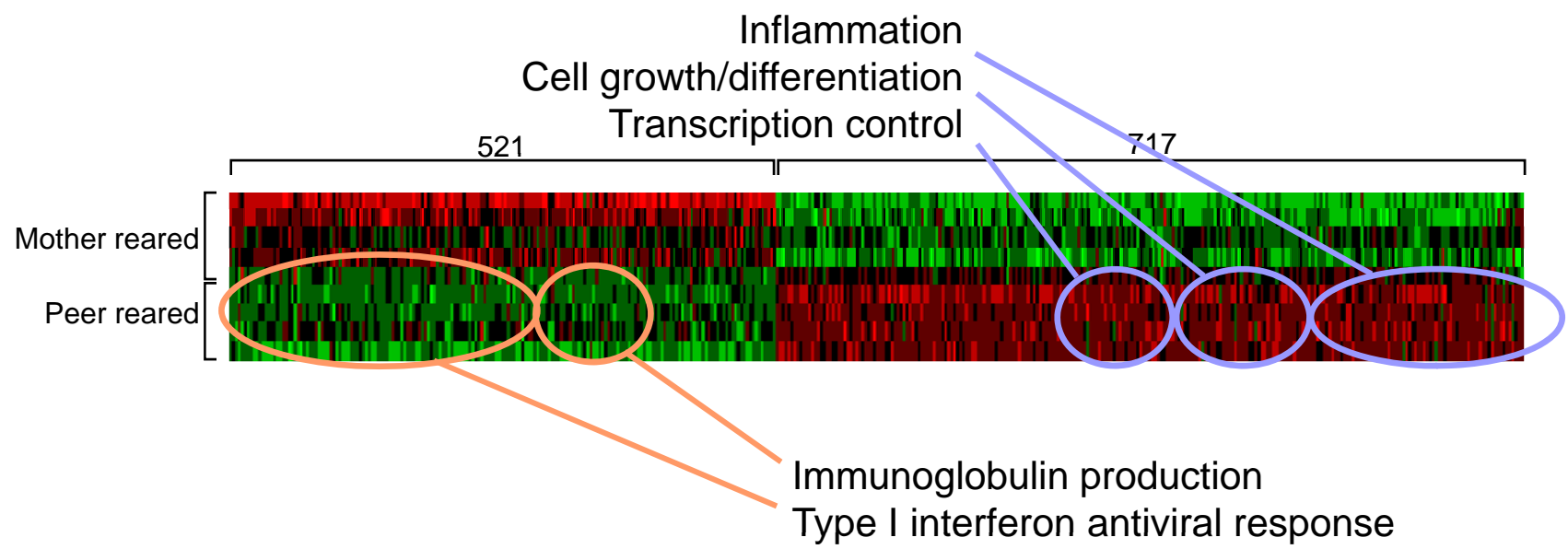
Early life social conditions

S. Suomi



Early life social conditions

S. Suomi



Low SES

Early life low SES

Social threat

Social loss / anticipated bereavement

Social instability

Adolescent role incongruity

Loneliness

Introversion

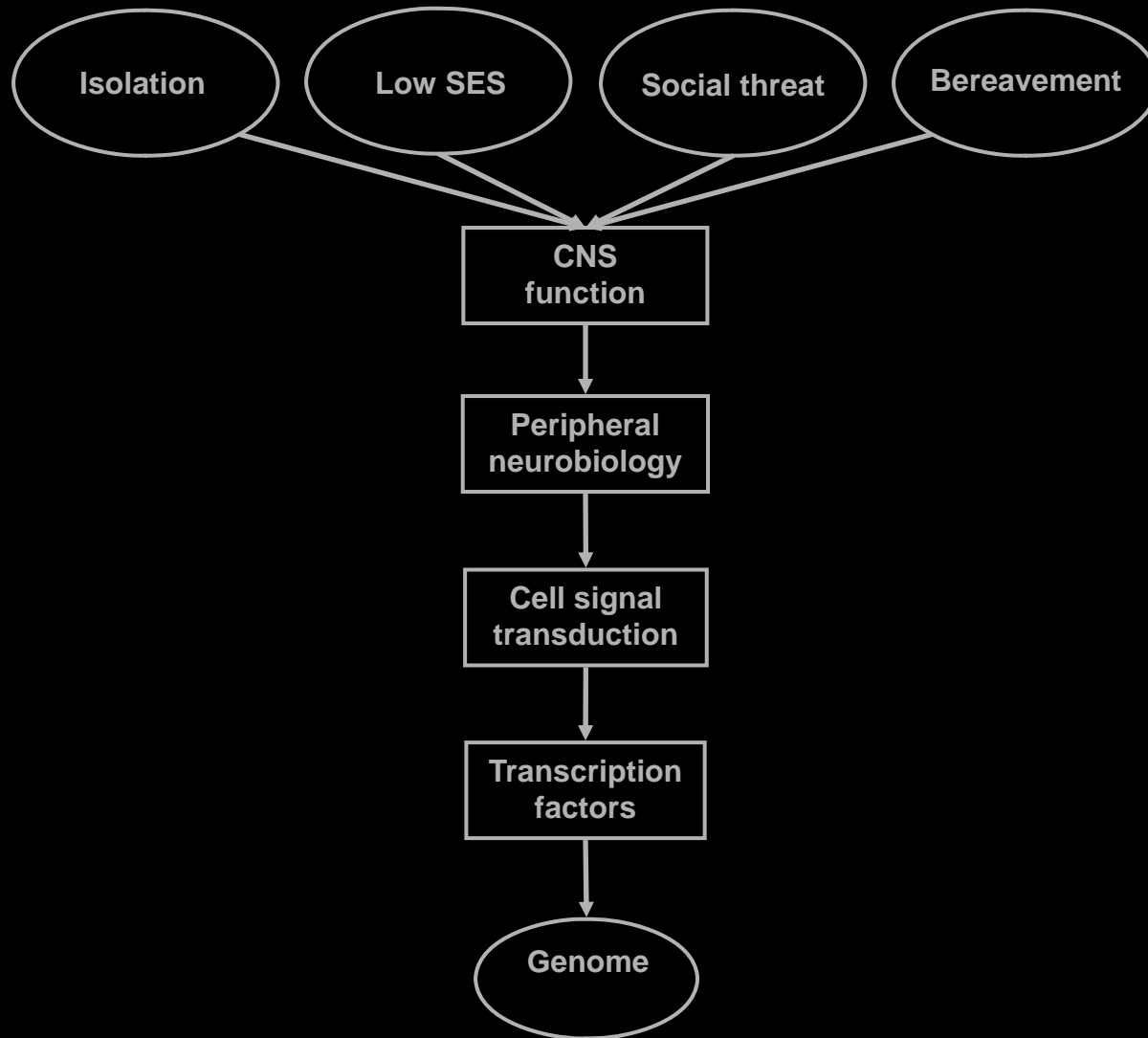
Acute stress

Chronic stress

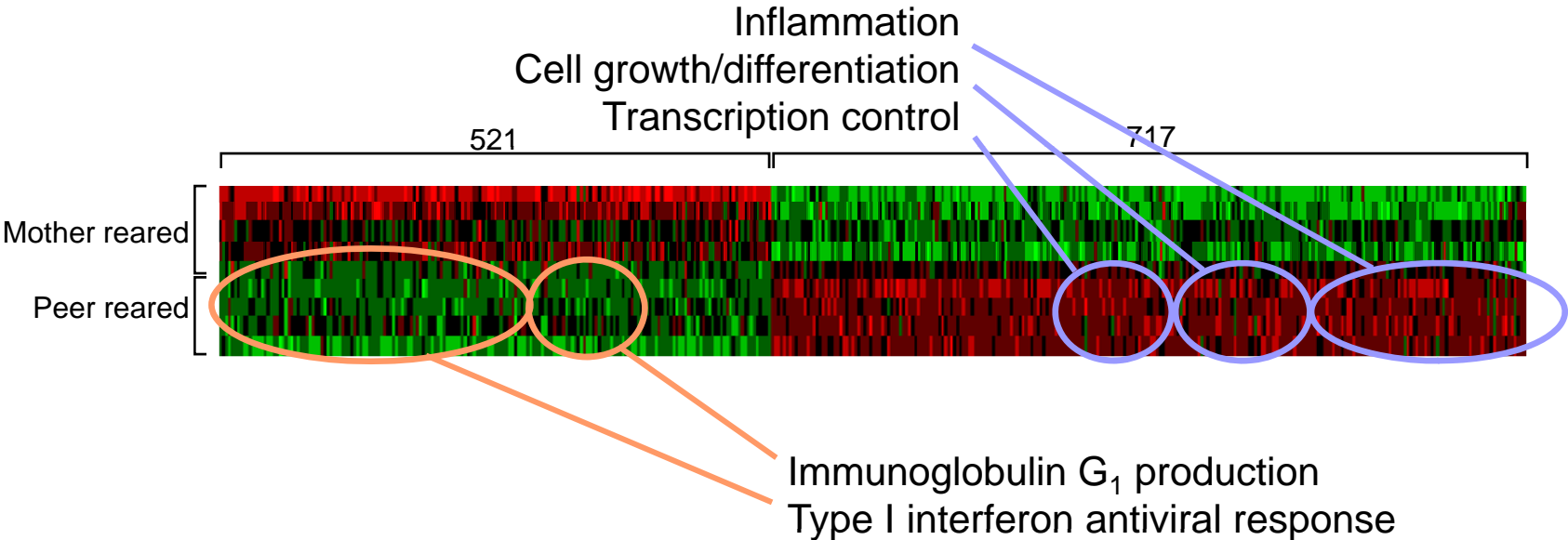
Depression

Sleep loss

Social signal transduction



CTRA – conserved transcriptional response to adversity



CTRA – conserved transcriptional response to adversity

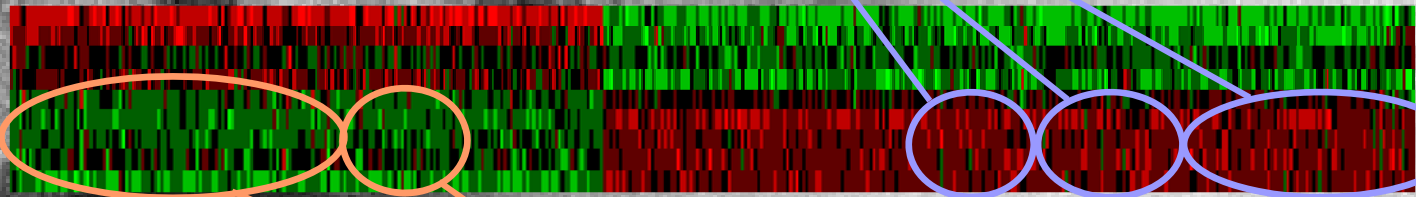
Inflammation
Cell growth/differentiation
Transcription control

521

717

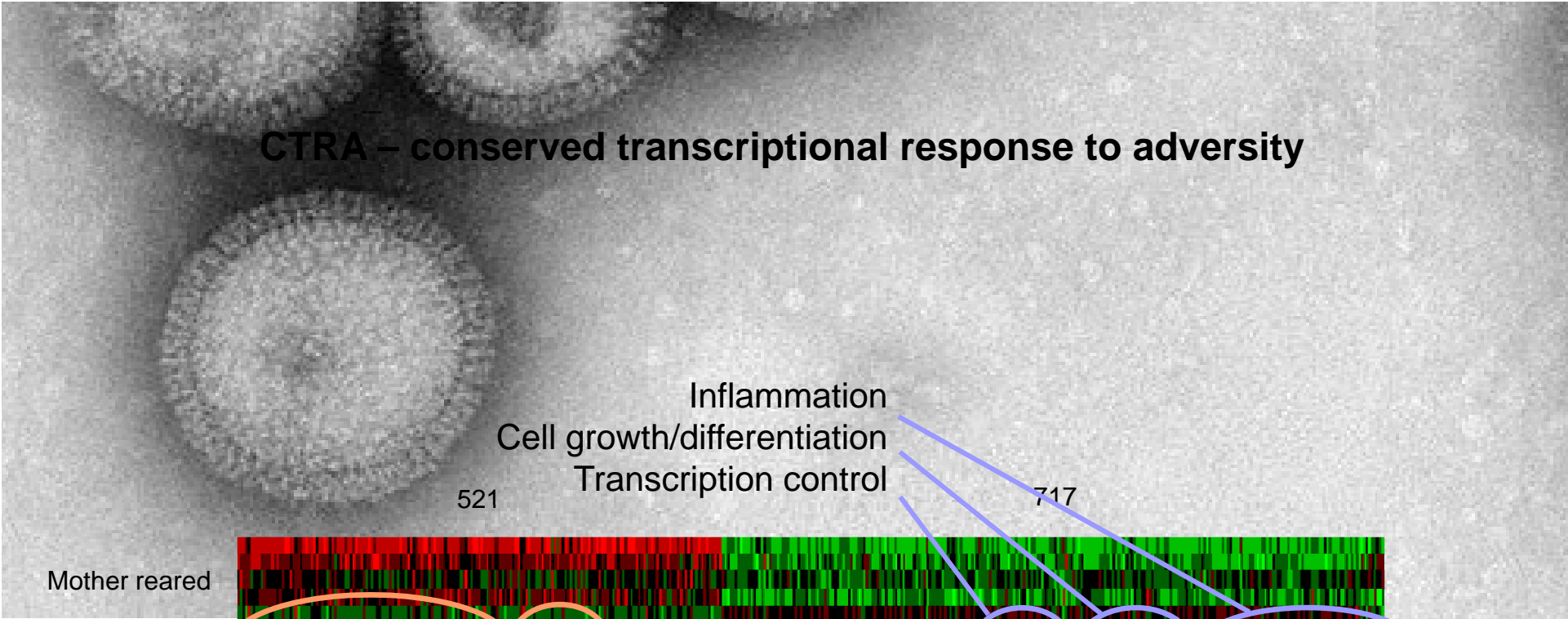
Mother reared

Peer reared



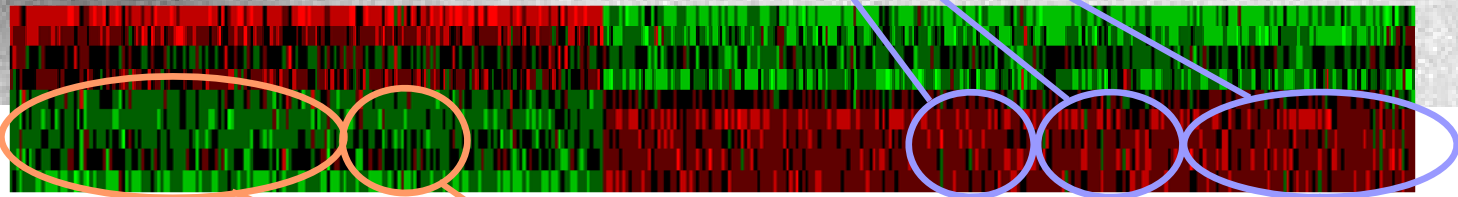
Immunoglobulin G₁ production
Type I interferon antiviral response

CTRA – conserved transcriptional response to adversity



Mother reared

Peer reared



Immunoglobulin G₁ production
Type I interferon antiviral response

CTRA – conserved transcriptional response to adversity

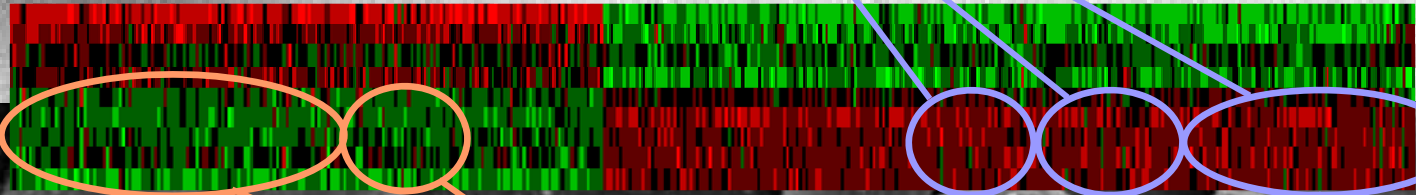
Inflammation
Cell growth/differentiation
Transcription control

521

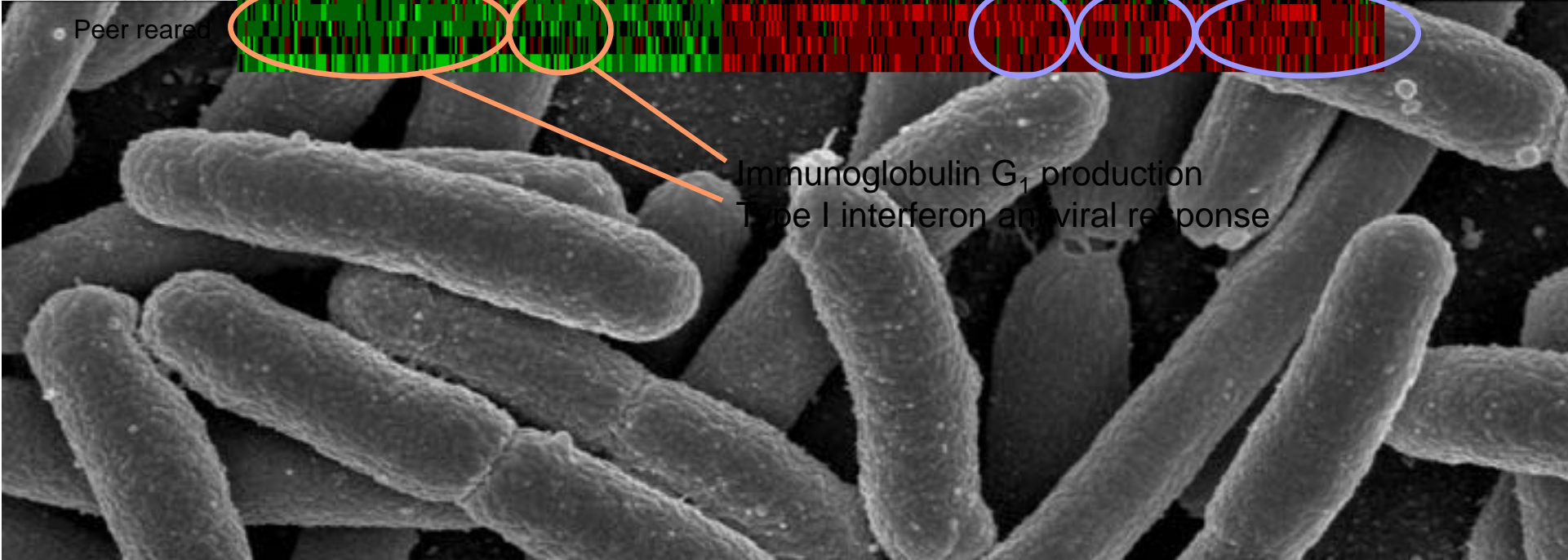
717

Mother reared

Peer reared



Immunoglobulin G₁ production
Type I interferon antiviral response



hate = bacteria

hate = bacteria

loneliness = predation

hate = bacteria

**loneliness = predation
= bacteria**

hate = bacteria

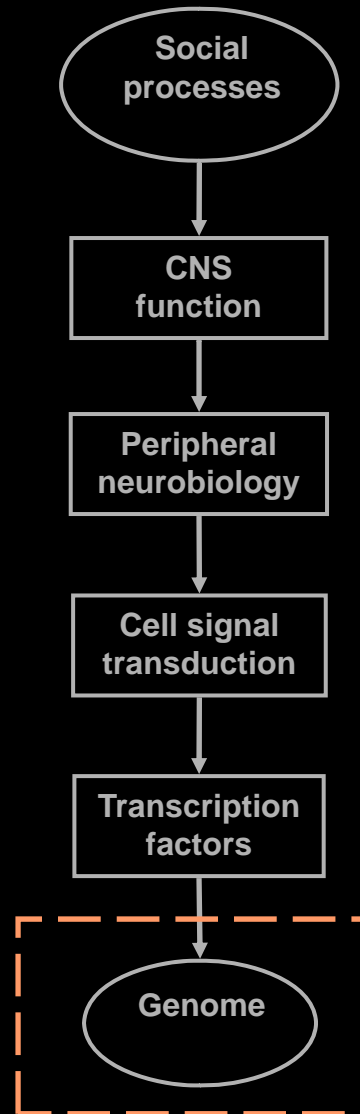
**loneliness = predation
= bacteria**

love = viruses

Social signal transduction

Simple questions

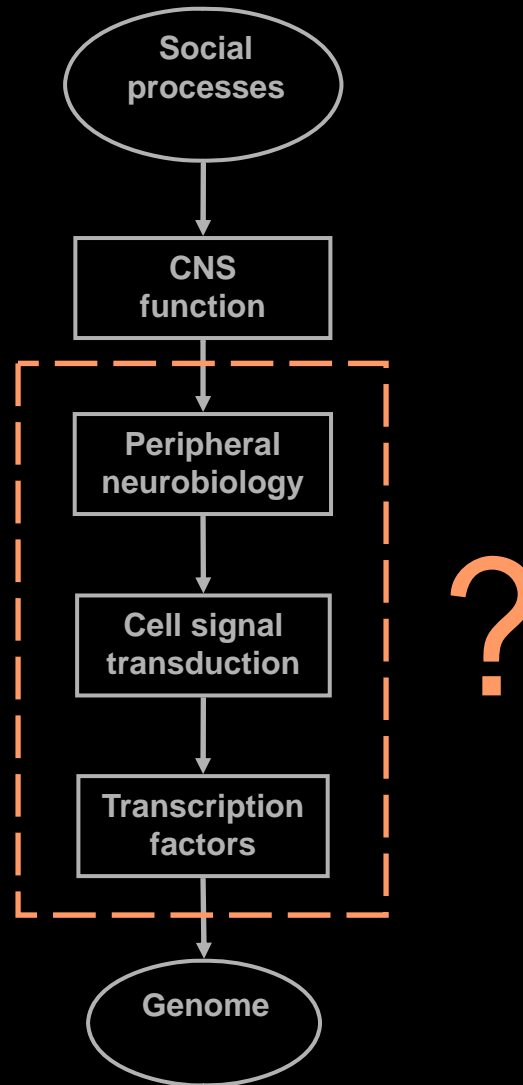
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?
3. Which genetic polymorphisms modulate social influences?



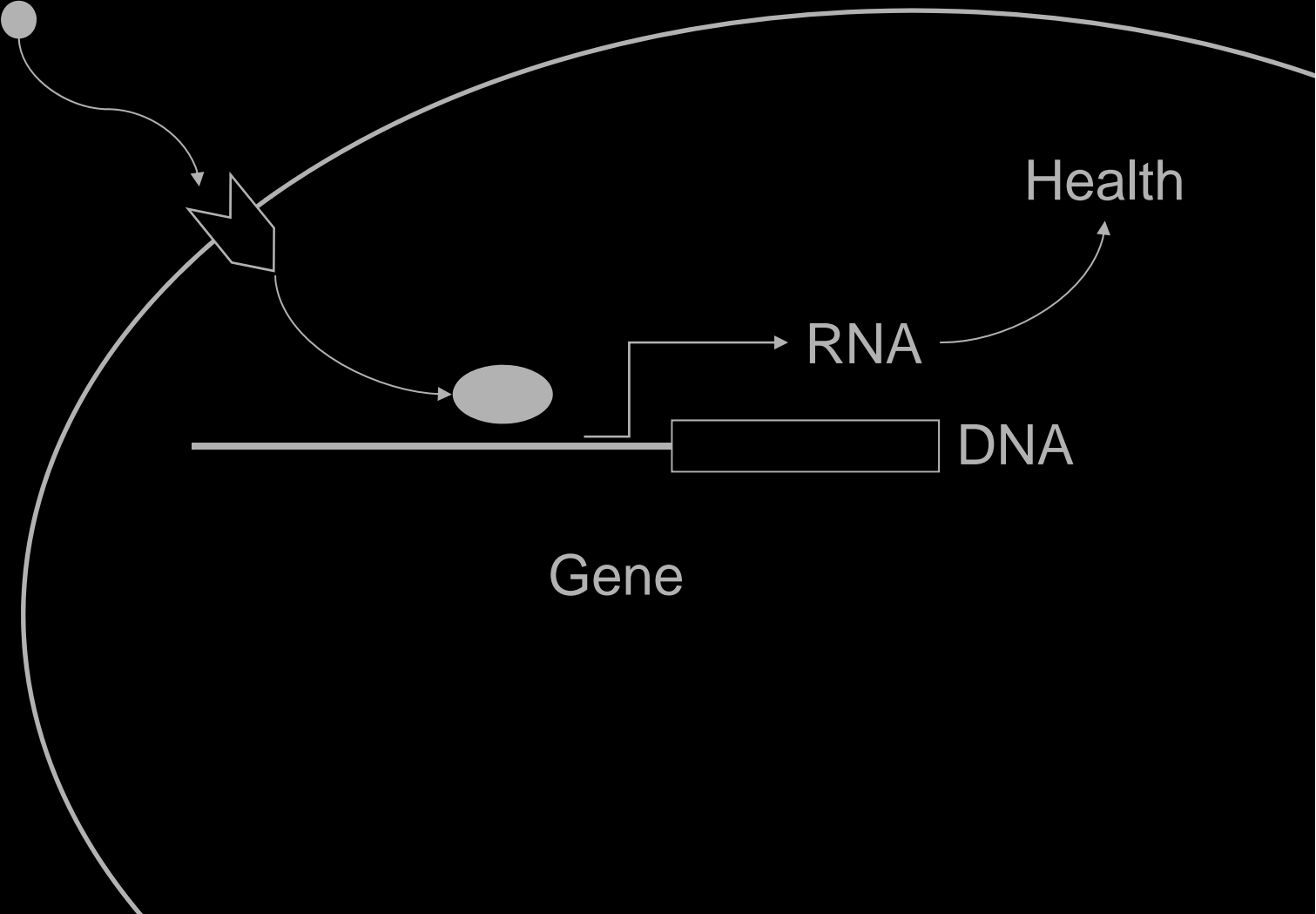
Social signal transduction

Simple questions

1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?
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Social Environment



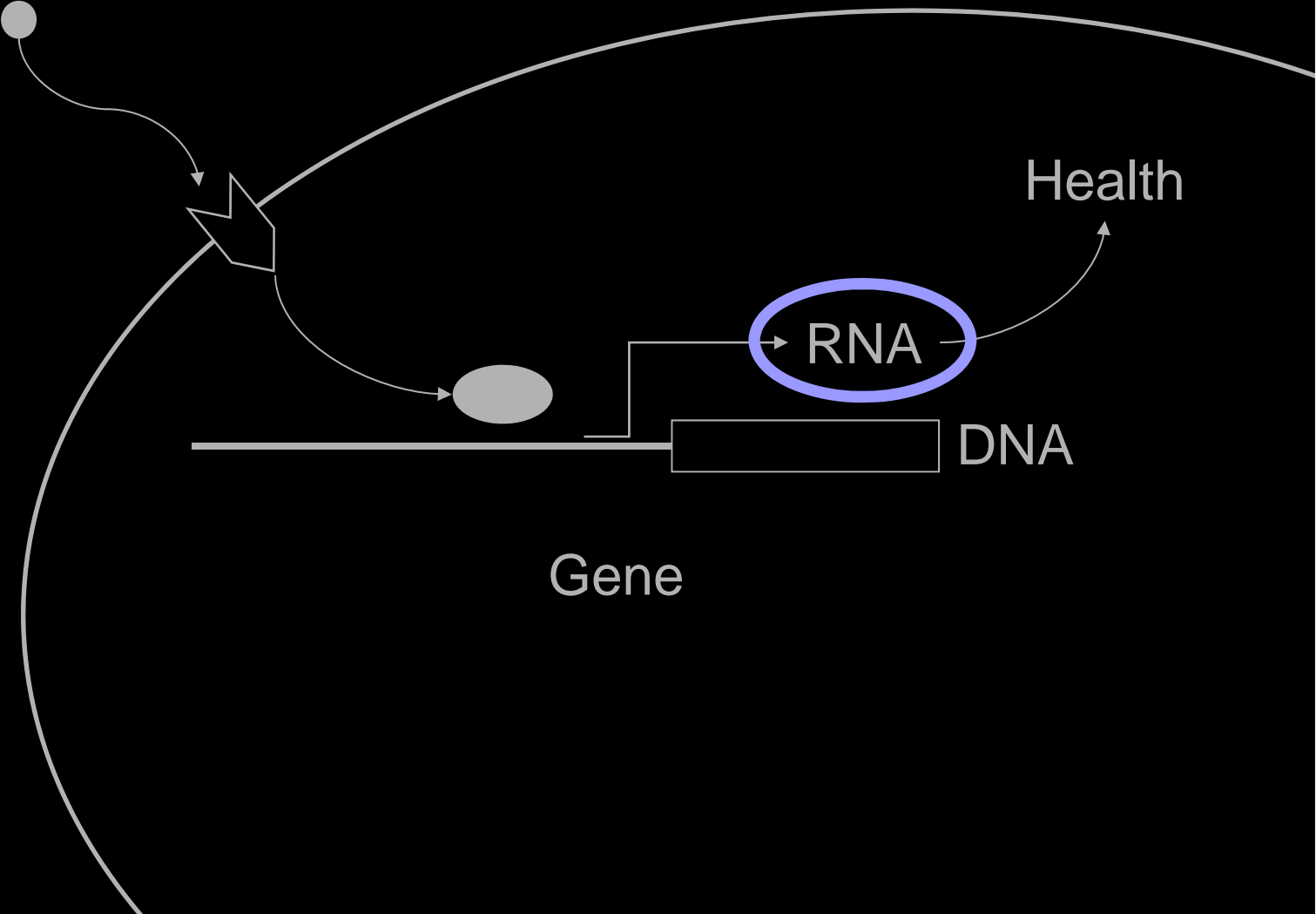
Health

RNA

DNA

Gene

Social Environment



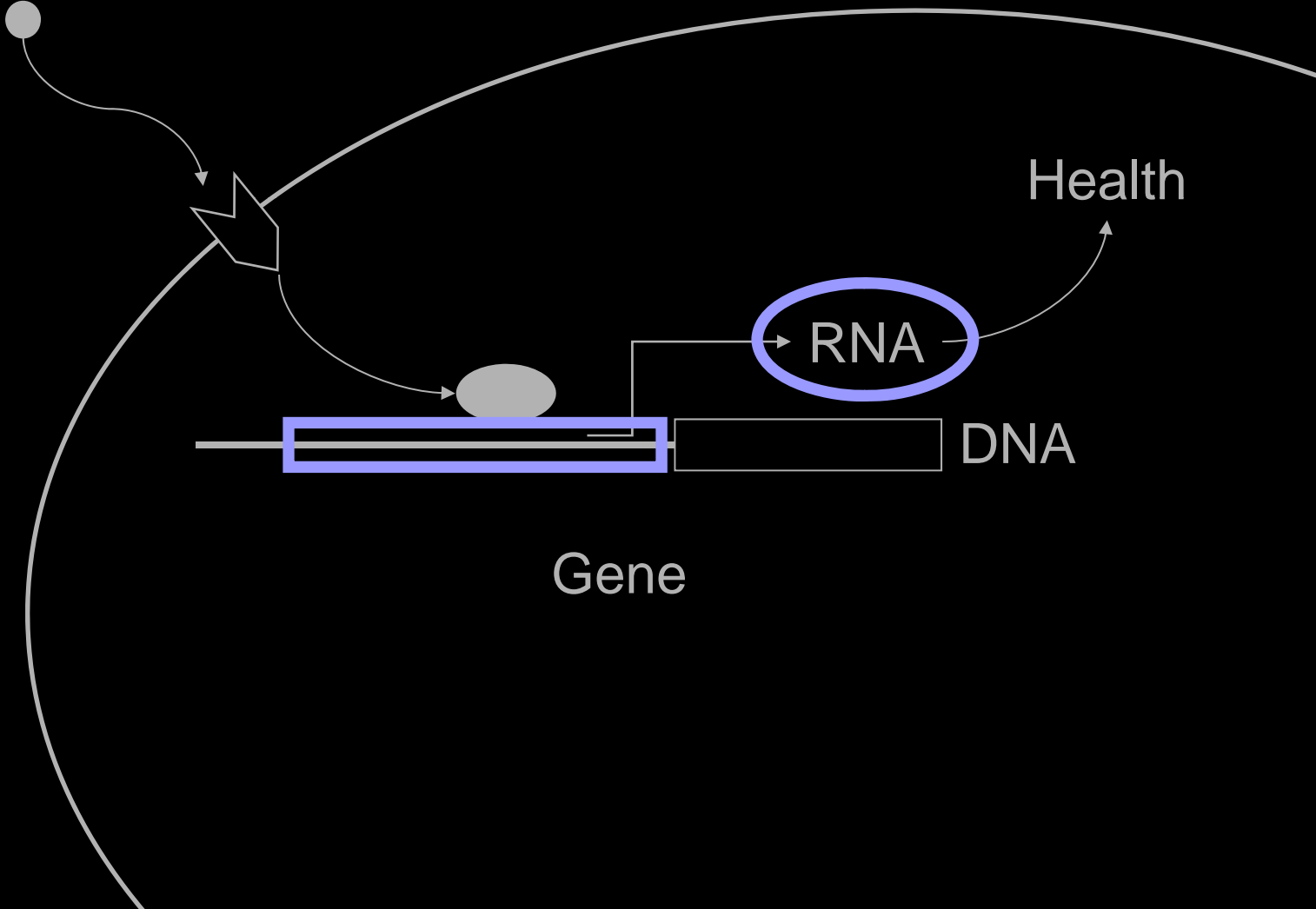
Health

RNA

DNA

Gene

Social Environment



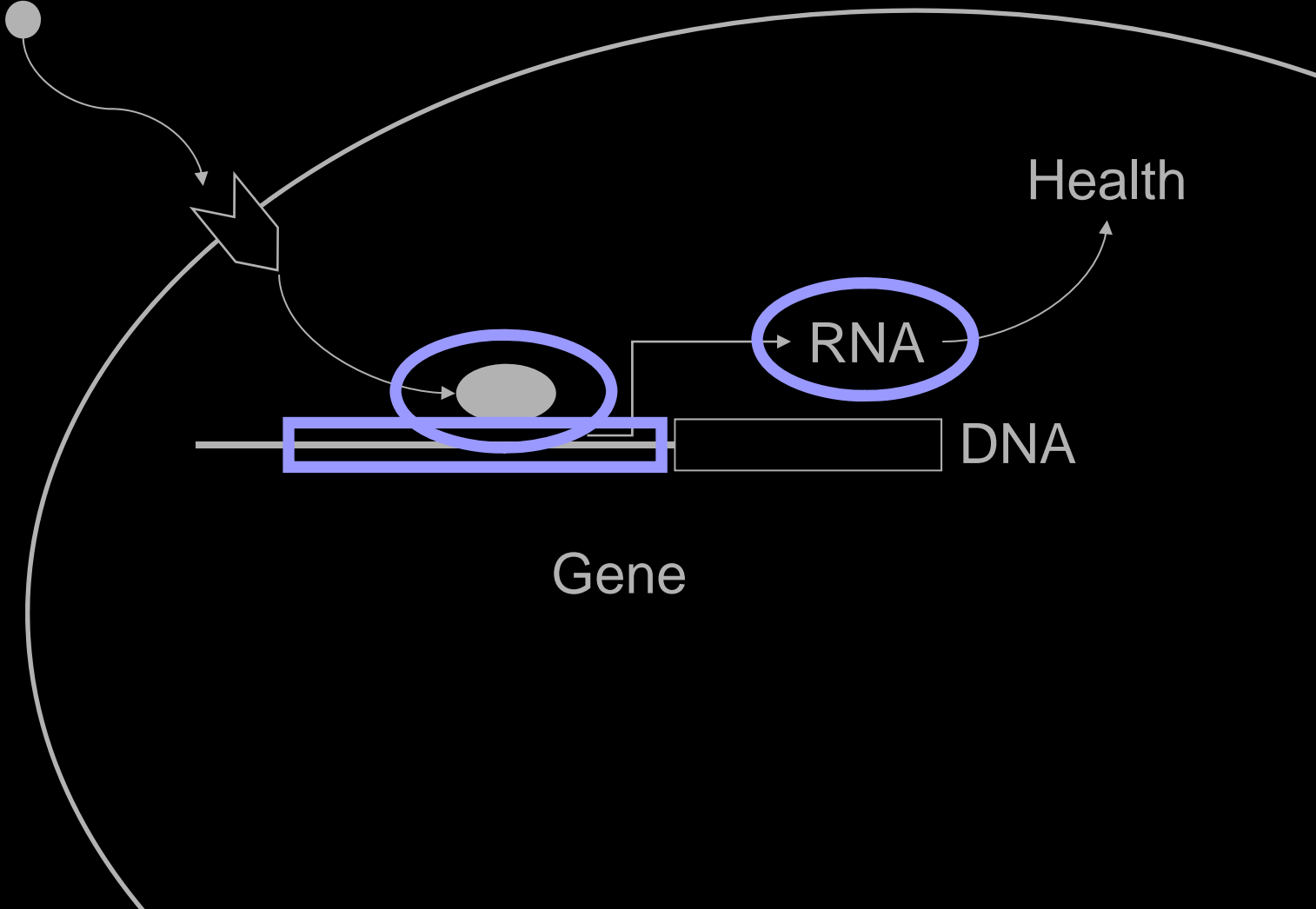
Health

RNA

DNA

Gene

Social Environment



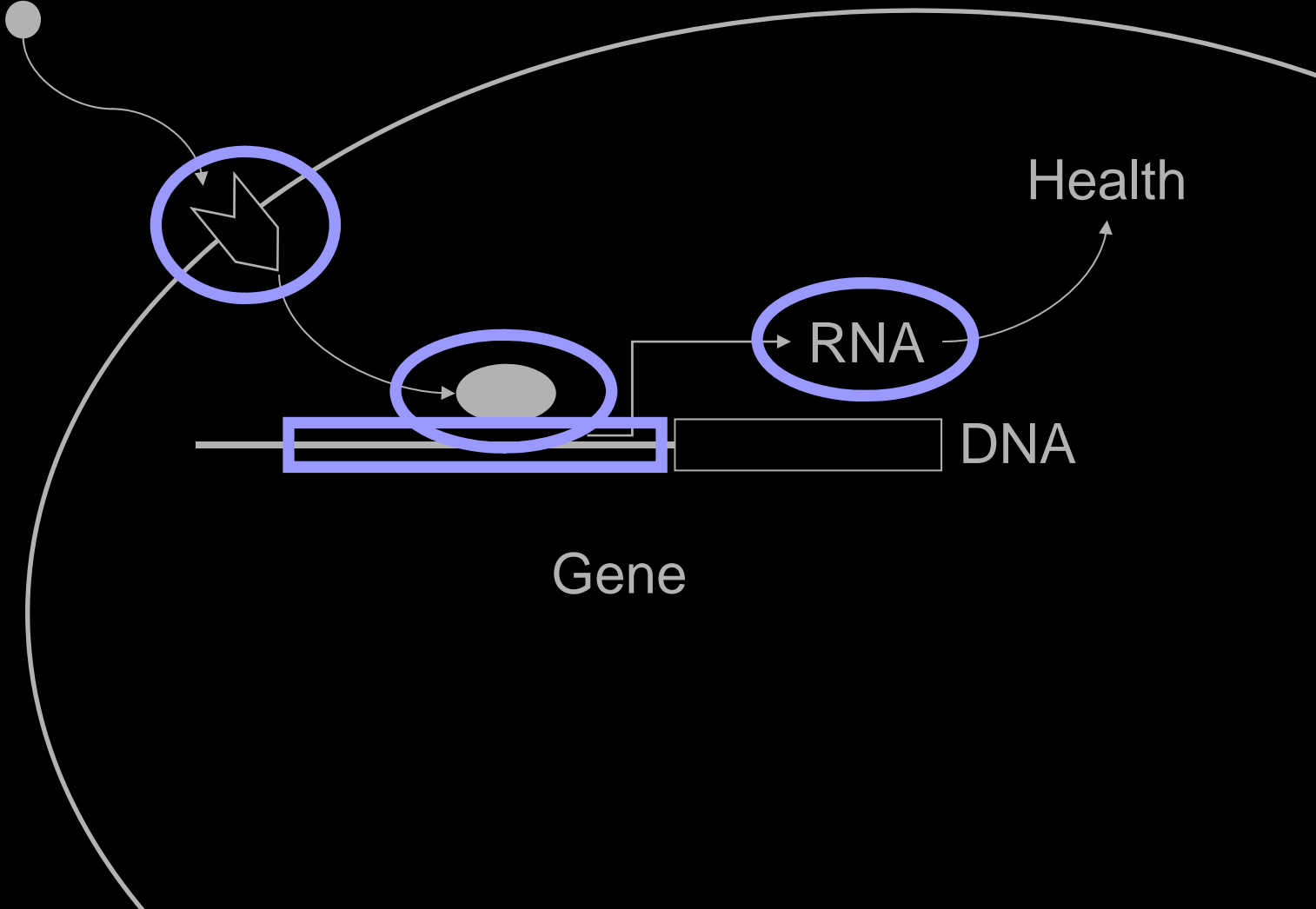
Health

RNA

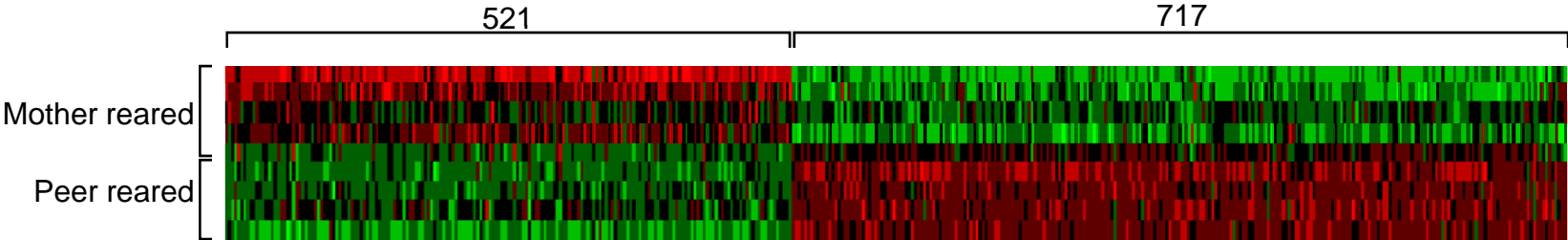
DNA

Gene

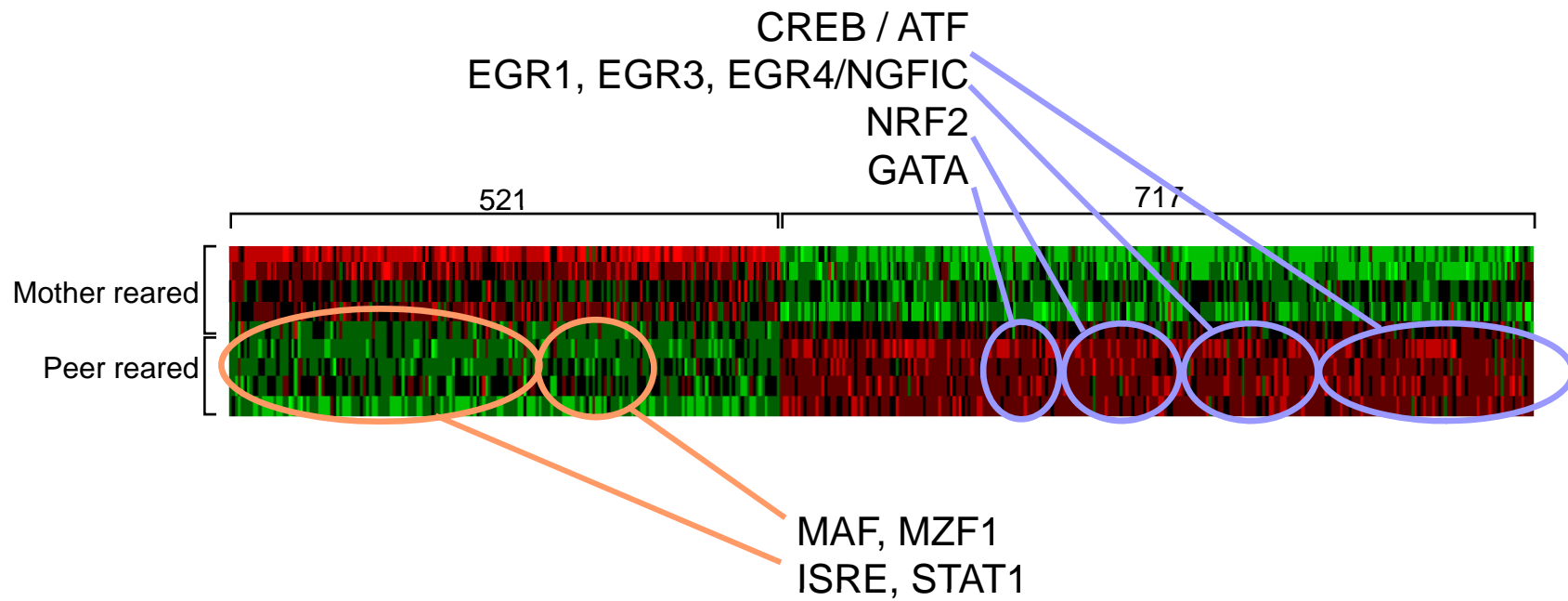
Social Environment



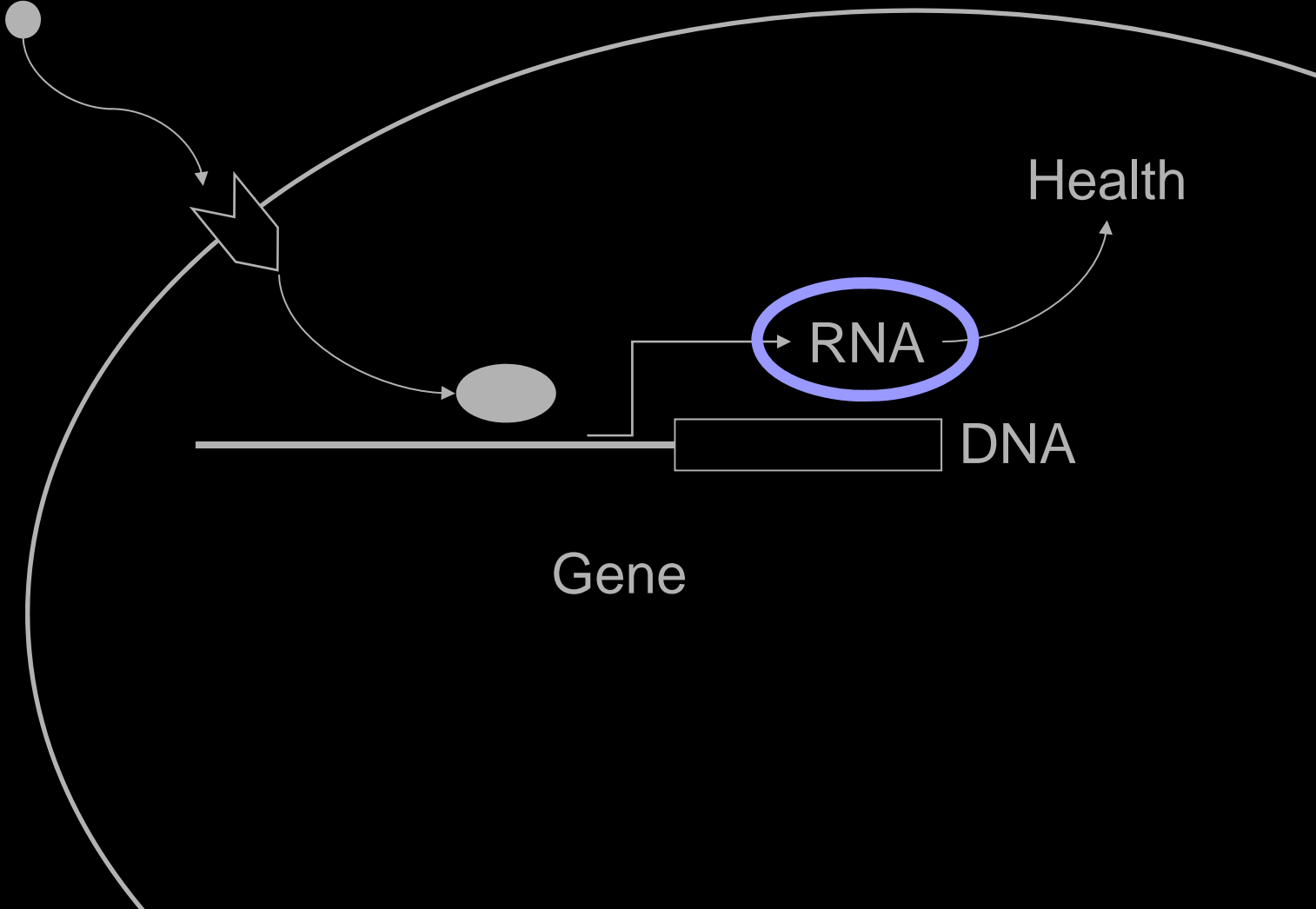
Early life social conditions



Early life social conditions



Social Environment



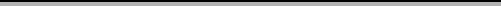
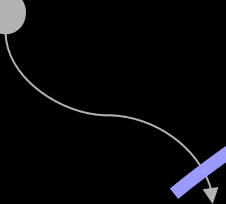
Health

RNA

DNA

Gene

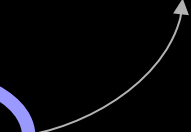
Social Environment



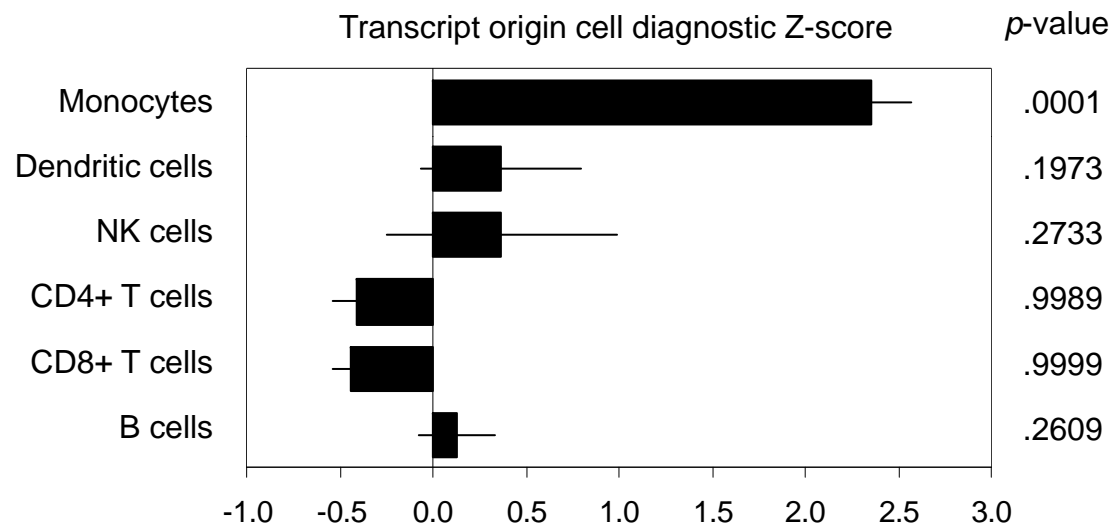
DNA

Gene

Health



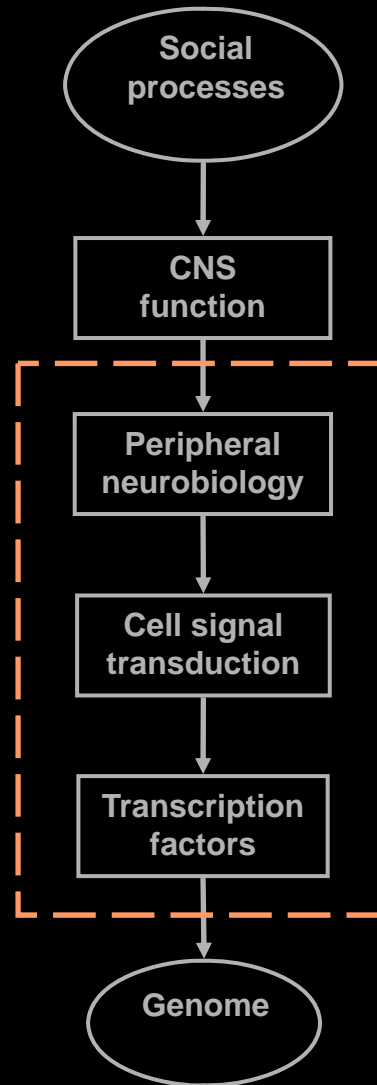
Immune cell target of social adversity



Social signal transduction

Simple questions

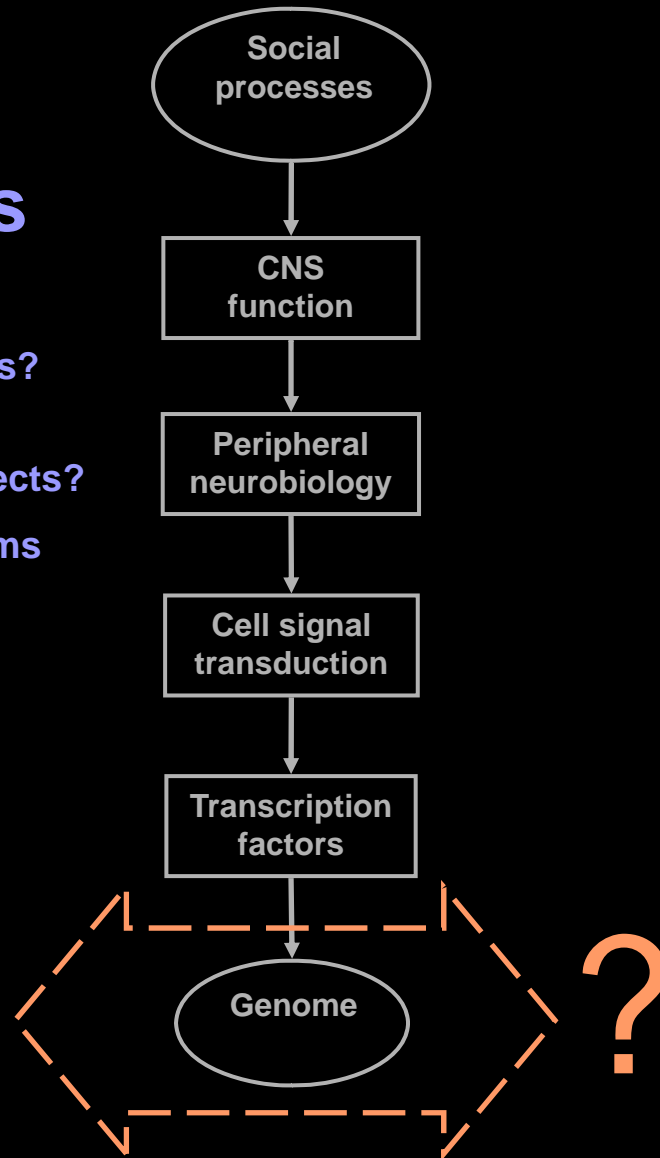
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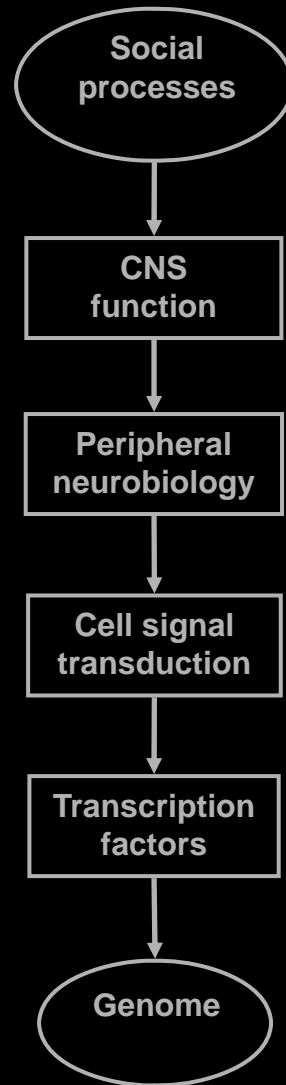
Social signal transduction

Simple questions

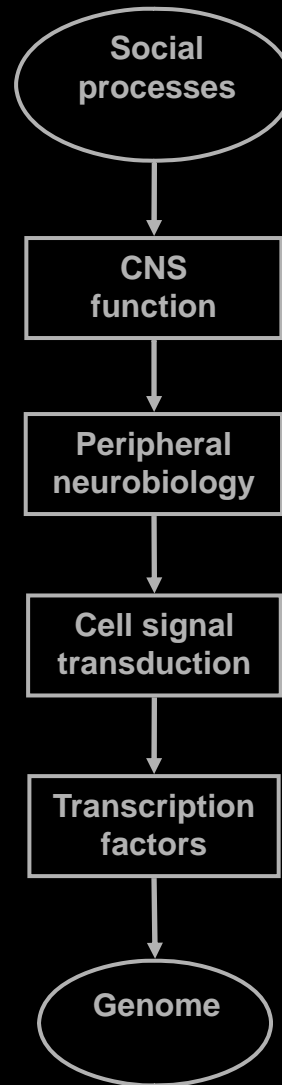
1. Which gene modules are sensitive to social processes?
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System properties

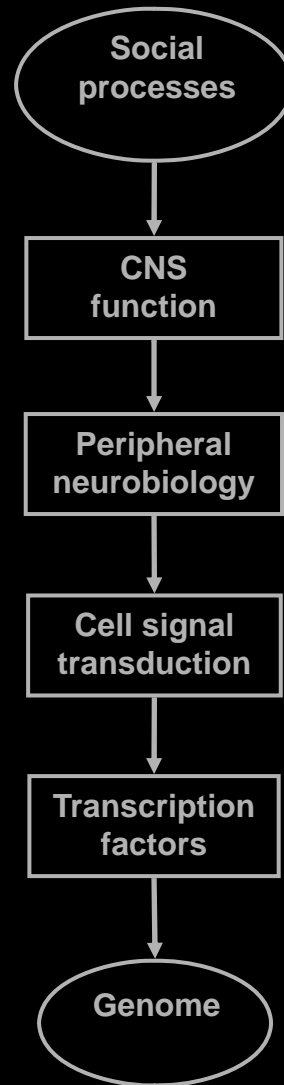


System properties



1. Subjectivity

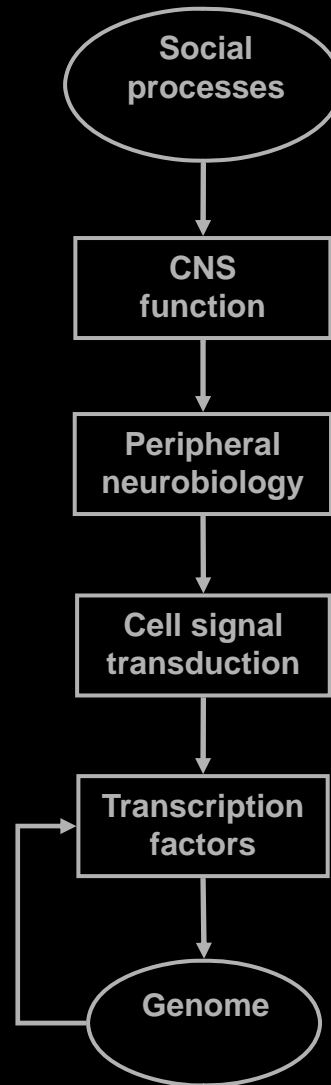
System properties



1. Subjectivity

2. Basal remodeling

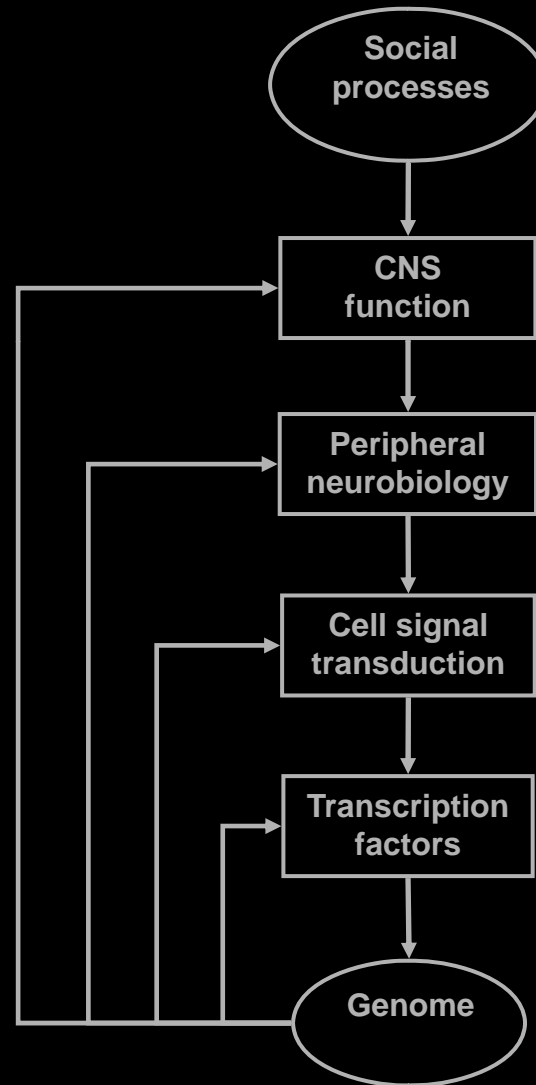
System properties



1. Subjectivity

2. Basal remodeling

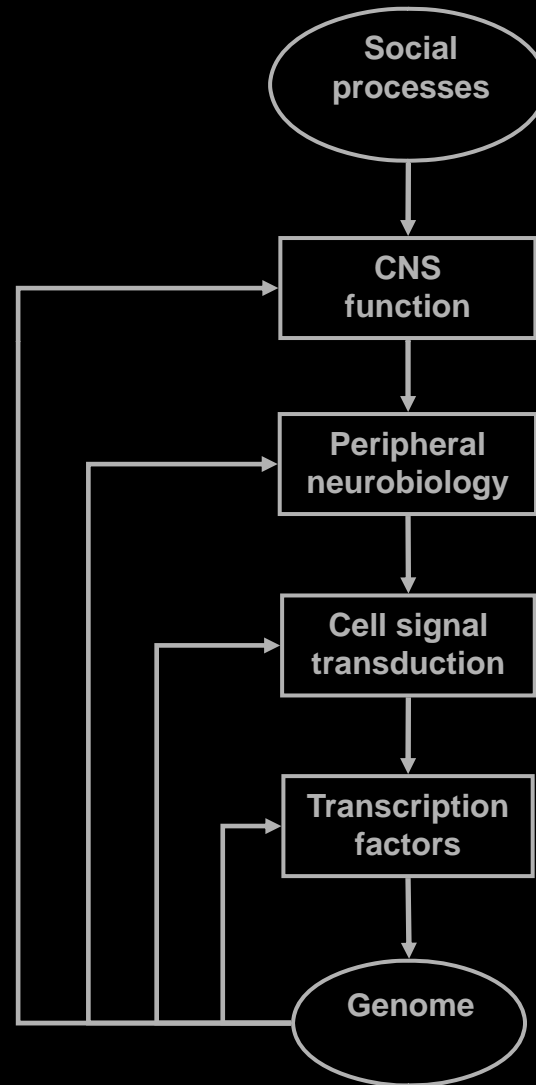
System properties



1. Subjectivity

2. Basal remodeling

System properties



1. Subjectivity

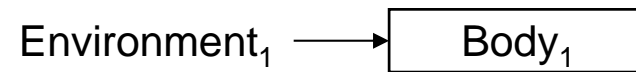
3. Recursive persistence

2. Basal remodeling

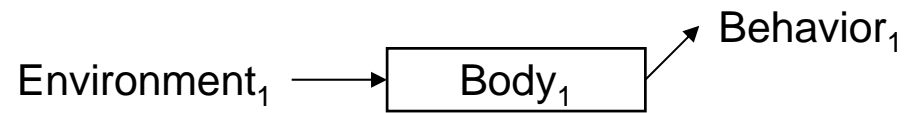
Recursive developmental remodeling

Body₁

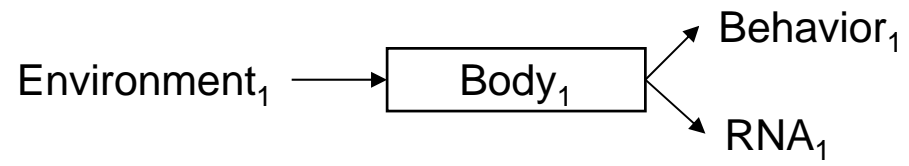
Recursive developmental remodeling



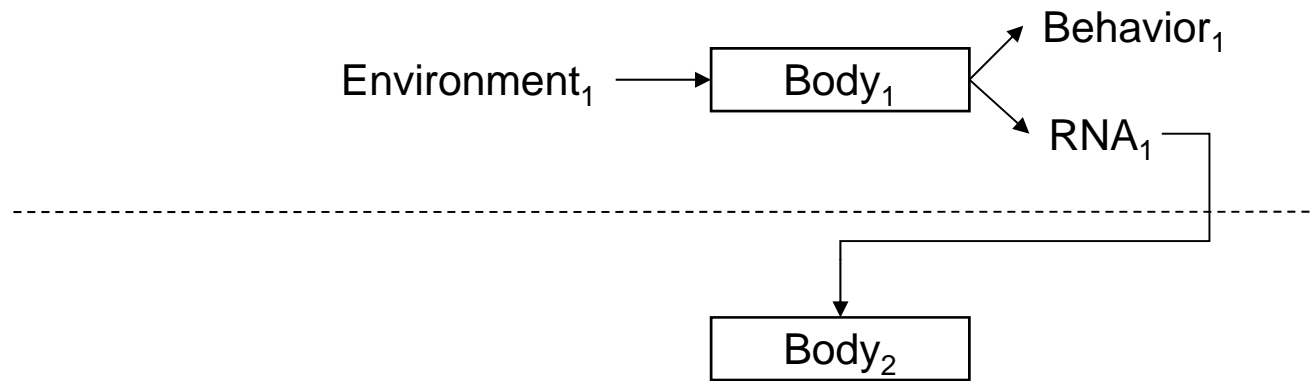
Recursive developmental remodeling



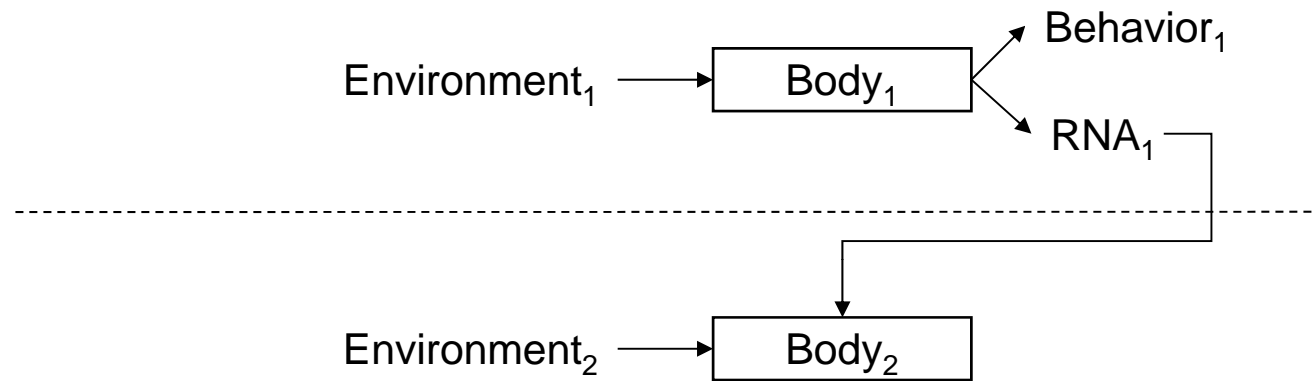
Recursive developmental remodeling



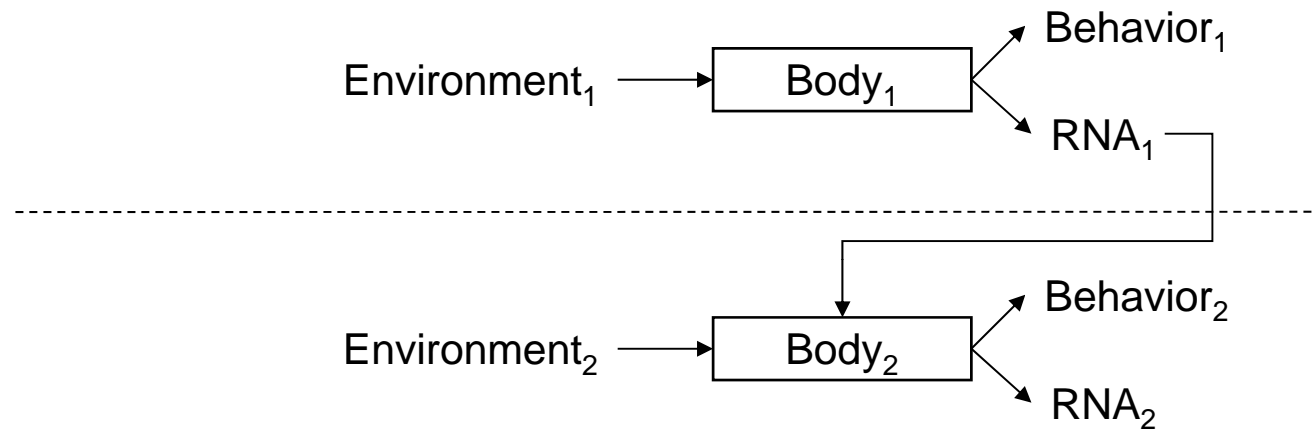
Recursive developmental remodeling



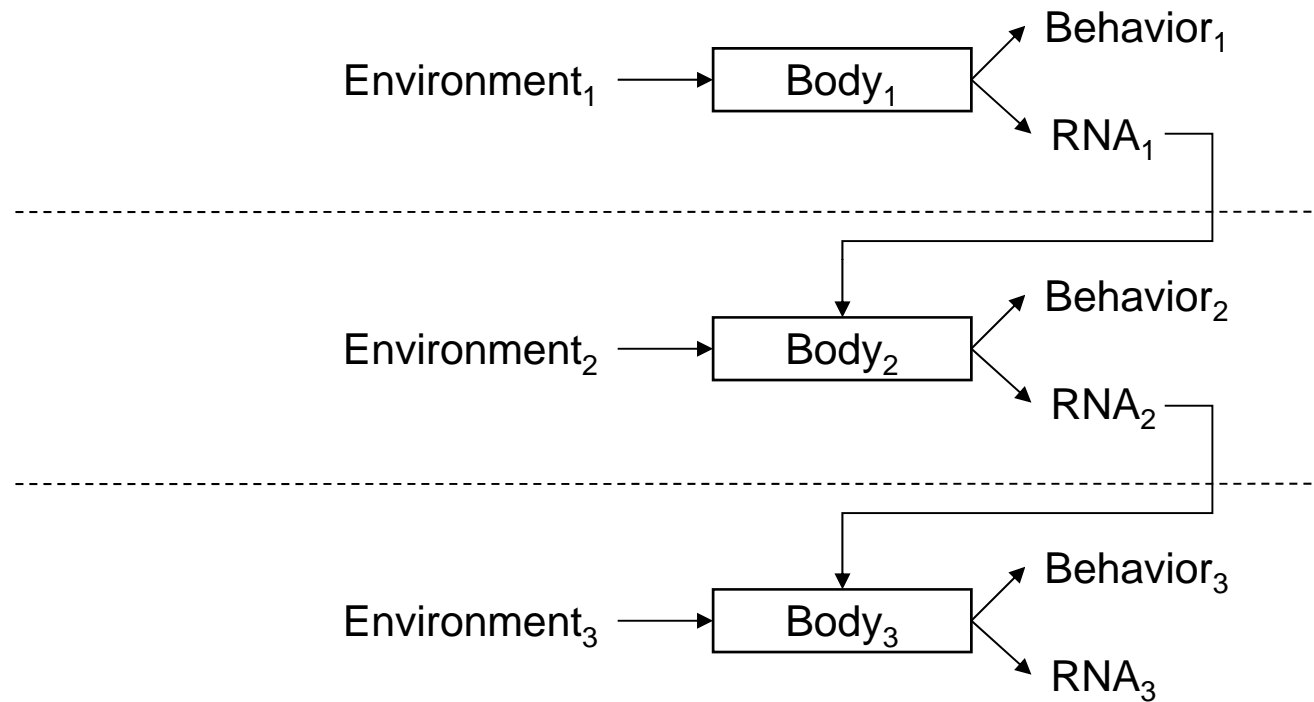
Recursive developmental remodeling



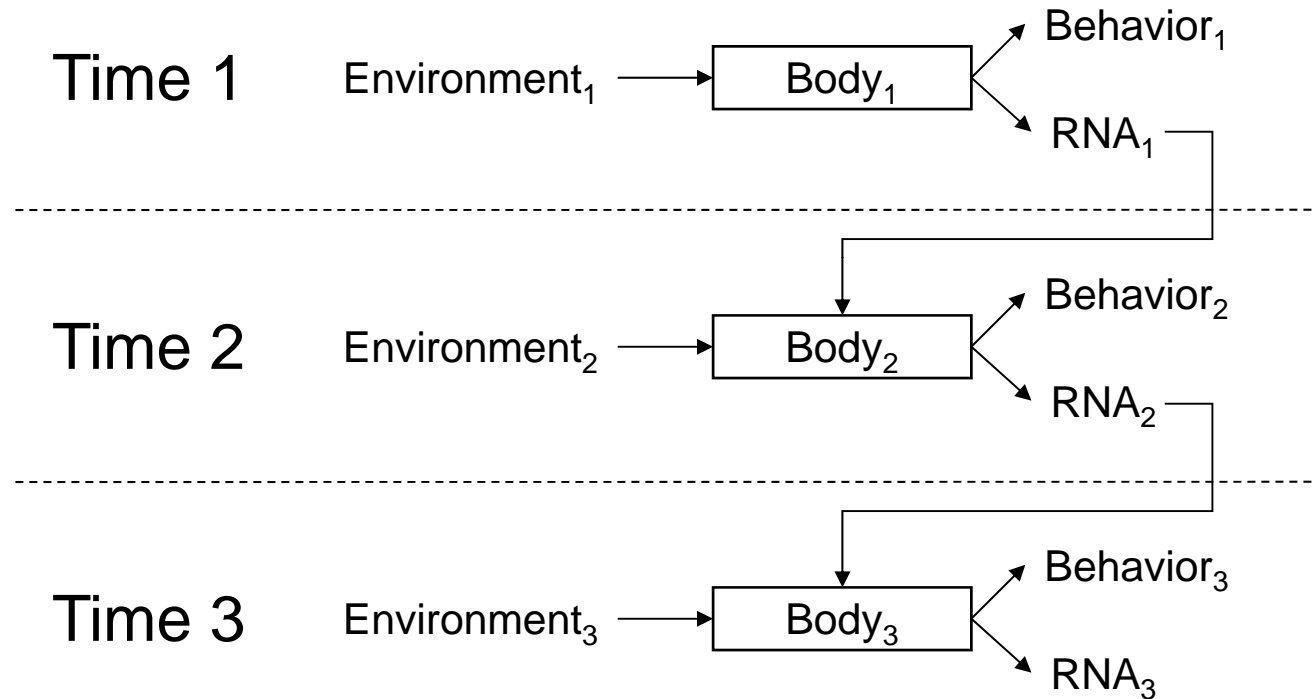
Recursive developmental remodeling



Recursive developmental remodeling

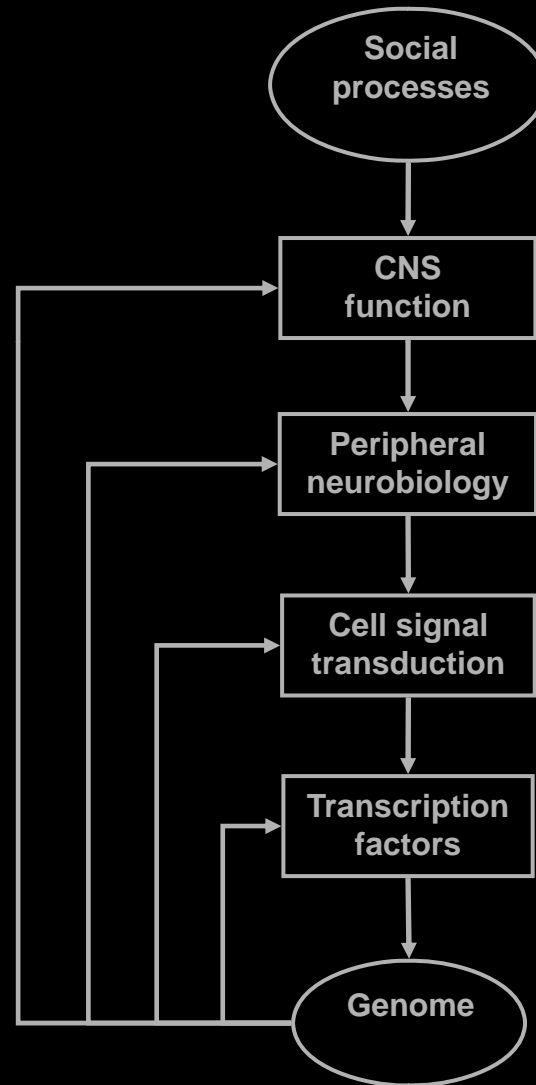


Recursive developmental remodeling



RNA = intra-organismic adaptation

System properties

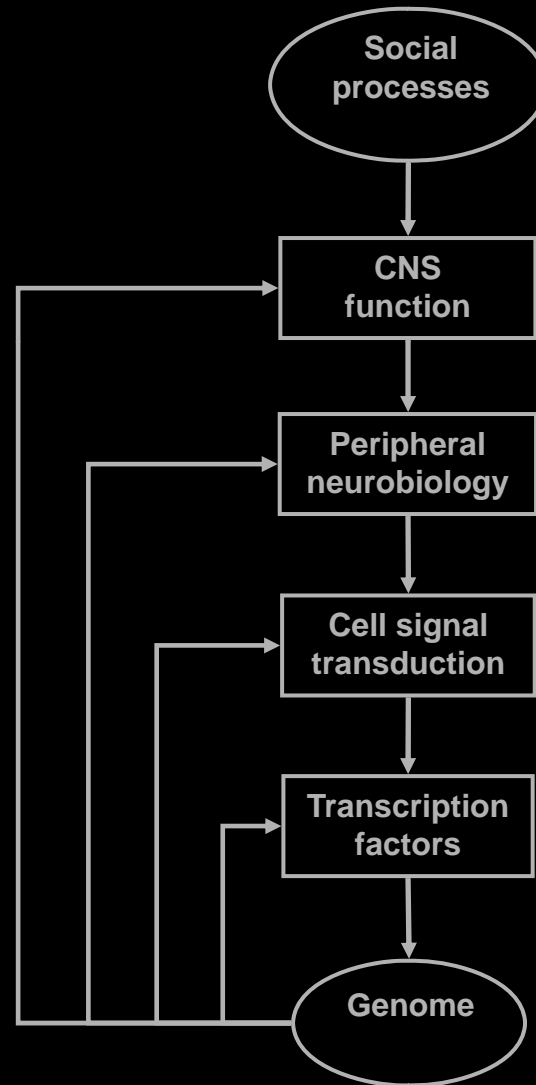


1. Subjectivity

3. Recursive persistence

2. Basal remodeling

System properties



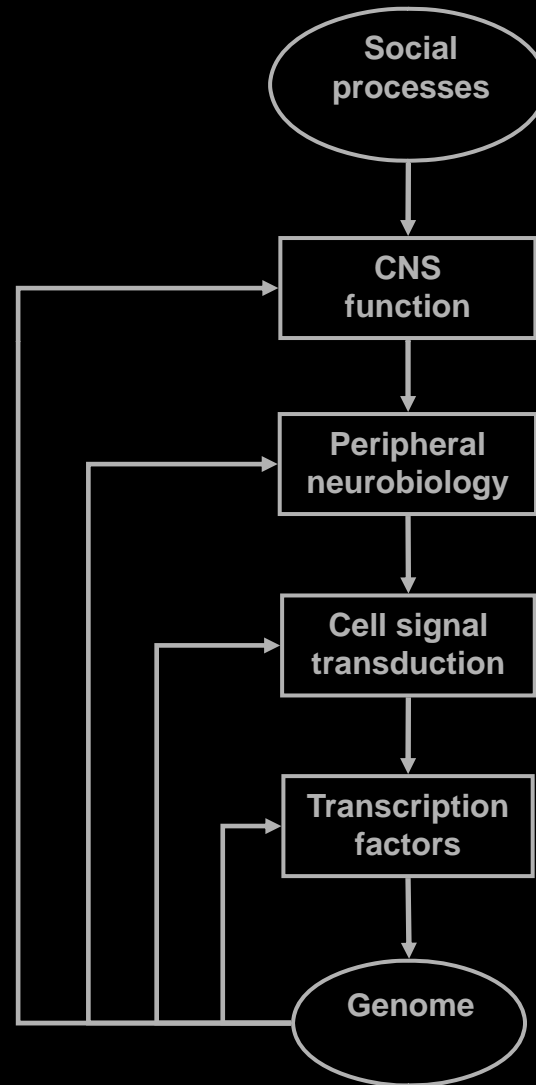
4. Environmental recursion

1. Subjectivity

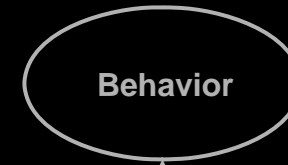
3. Recursive persistence

2. Basal remodeling

System properties



4. Environmental recursion



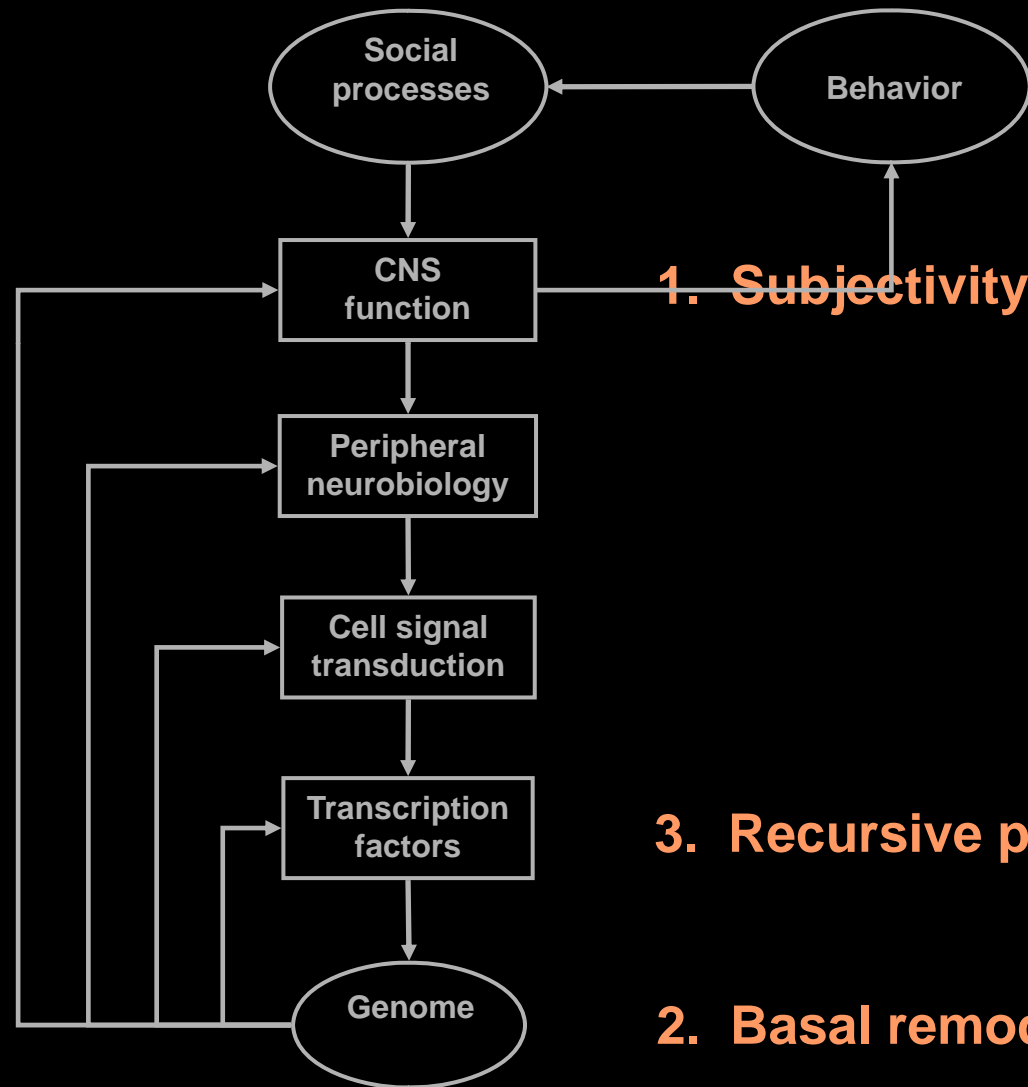
1. Subjectivity

3. Recursive persistence

2. Basal remodeling

System properties

4. Environmental recursion

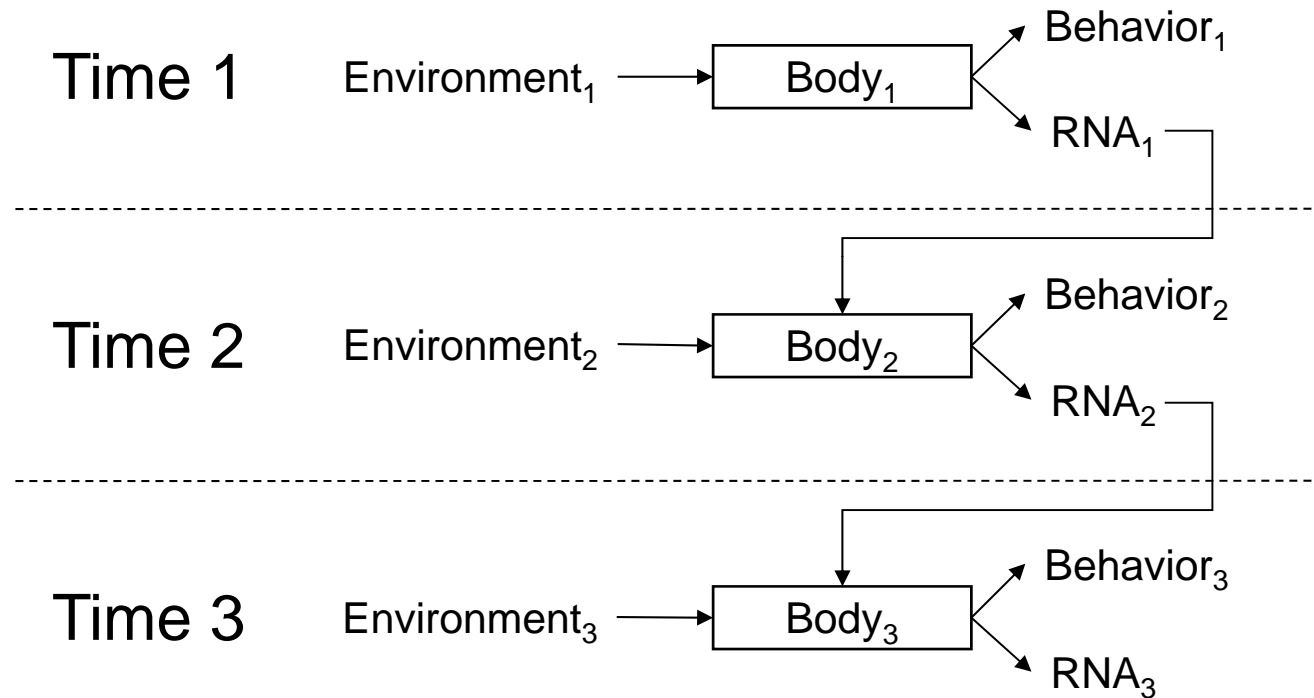


1. Subjectivity

3. Recursive persistence

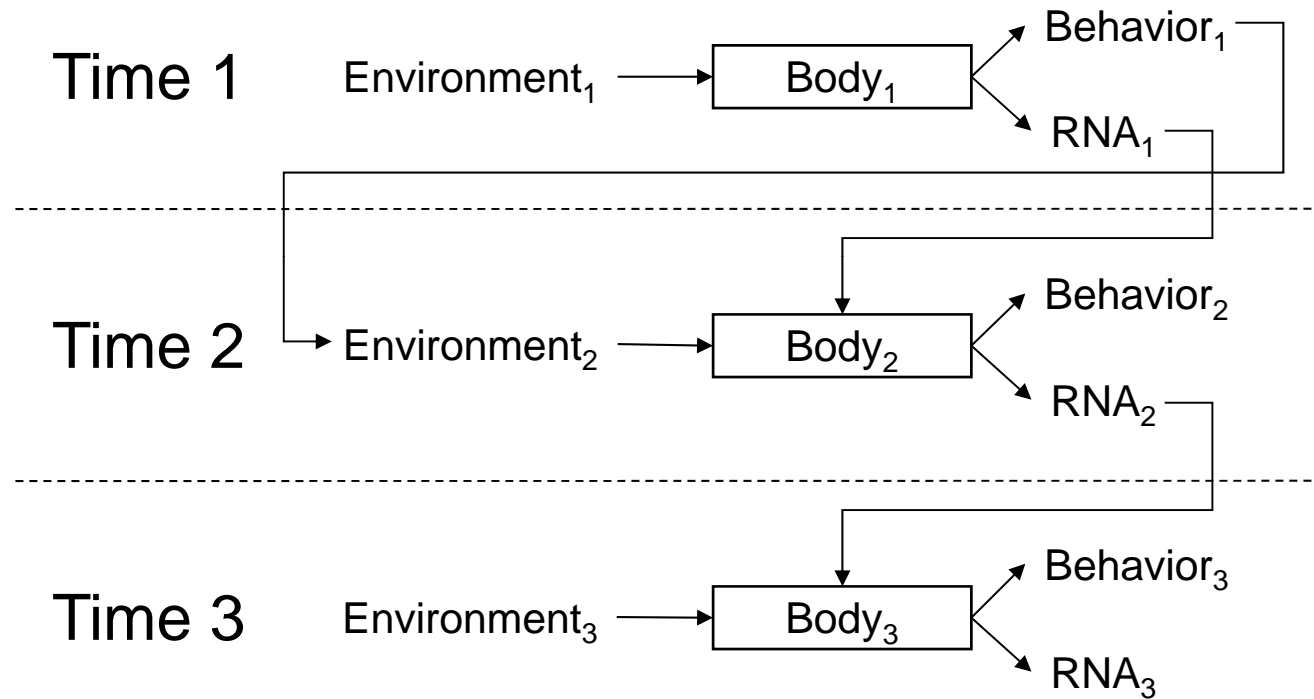
2. Basal remodeling

Recursive developmental remodeling



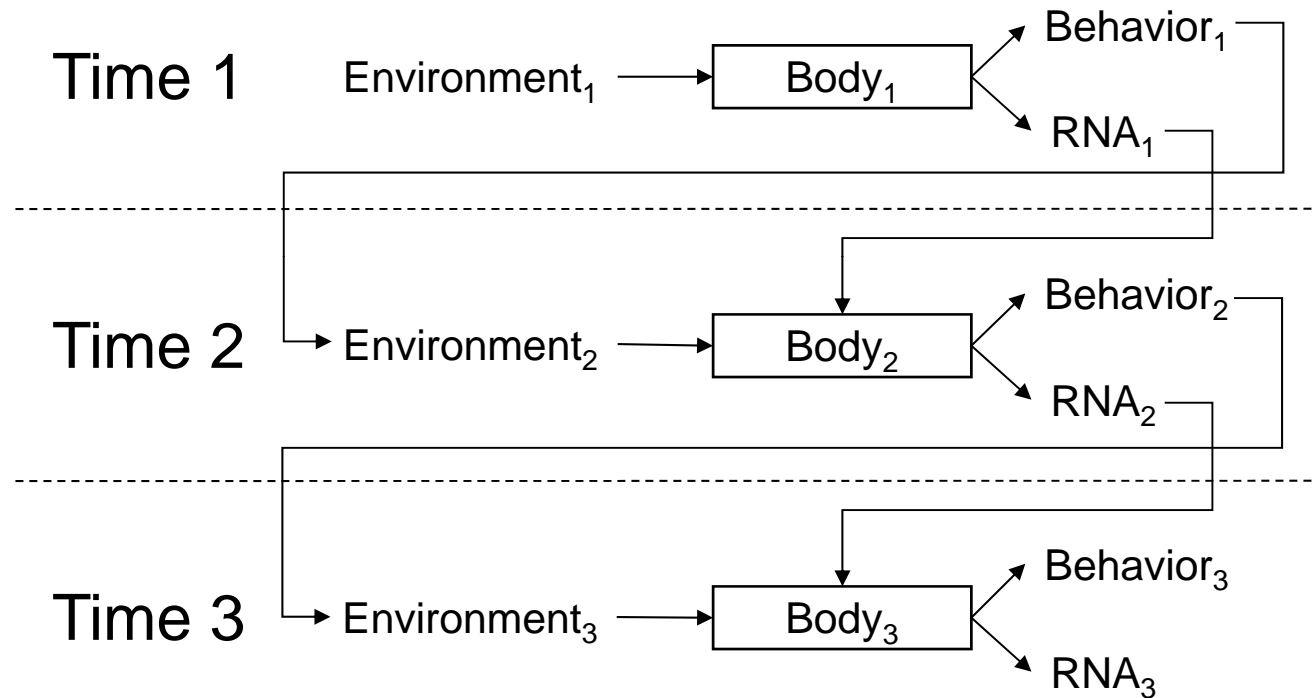
RNA = intra-organismic adaptation

Recursive developmental remodeling



RNA = intra-organismic adaptation

Recursive developmental remodeling



RNA = intra-organismic adaptation

Your experiences today
will influence the molecular composition of your body
for the next 2-3 months

Your experiences today
will influence the molecular composition of your body
for the next 2-3 months

... or perhaps the rest of your life.

Your experiences today
will influence the molecular composition of your body
for the next 2-3 months

... or perhaps the rest of your life.

Plan your day accordingly.

Collaborators

Steve Suomi, James Heckman
John Cacioppo, Louise Hawkley, Bob Rose
Greg Miller, Edith Chen
Susan Lutgendorf, Anil Sood
John Sheridan
John Capitanio, Erica Sloan
Mike Irwin, Patti Ganz, Julie Bower
Margaret Kemeny, Jerry Zack
Teresa Seeman, Andrew Fuligni

Support

NCI CA116778, CA110793, CA109298
NIAID AI33259, AI36554, AI49135, AI52737
NIA AG107265, AG033590, AG34679
NIMH MH00820, MH15750
NCRR RR020645
UC Universitywide AIDS Research Program
UCLA AIDS Institute
MacArthur Foundation
James Pendleton Charitable Trust
Santa Fe Institute for Complex Systems
Norman Cousins Center

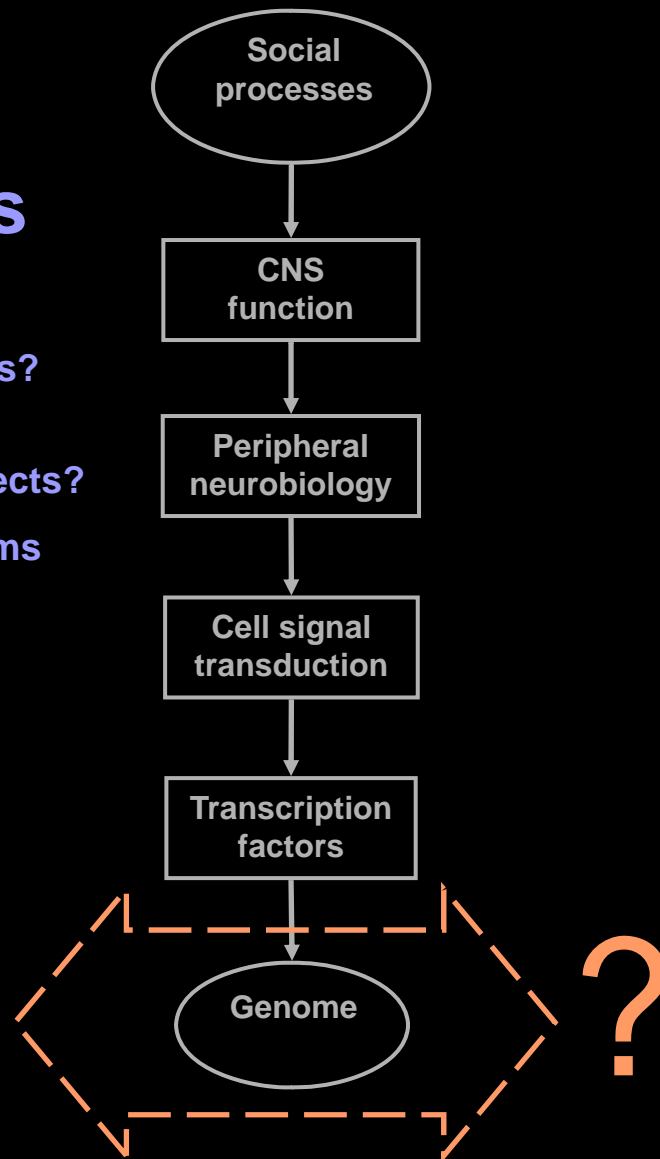




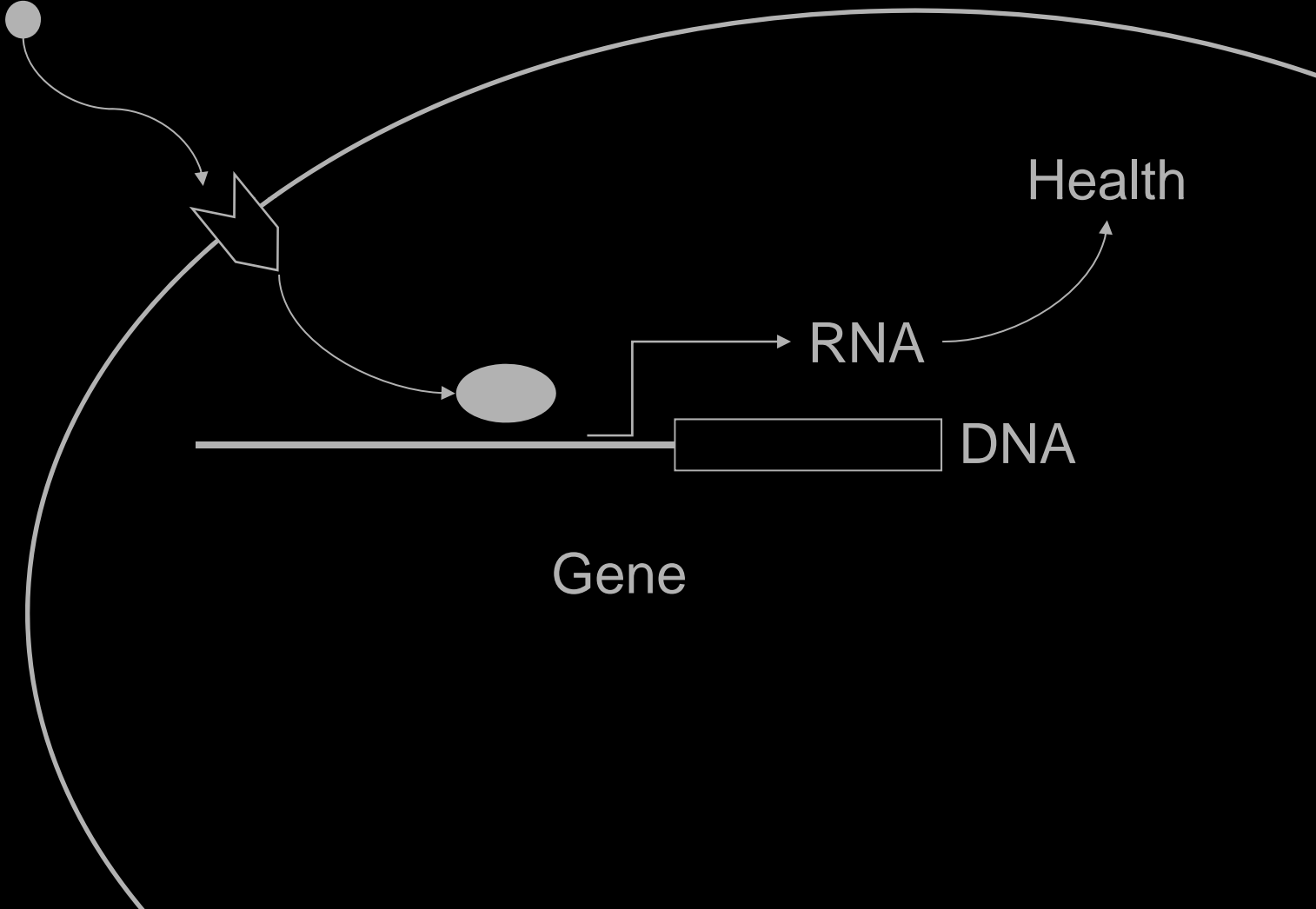
Social signal transduction

Simple questions

1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?
3. Which genetic polymorphisms modulate social influences?



Social Environment



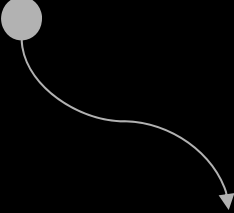
Health

RNA

DNA

Gene

Social Environment



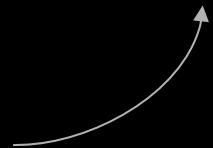
... [G/C] ...



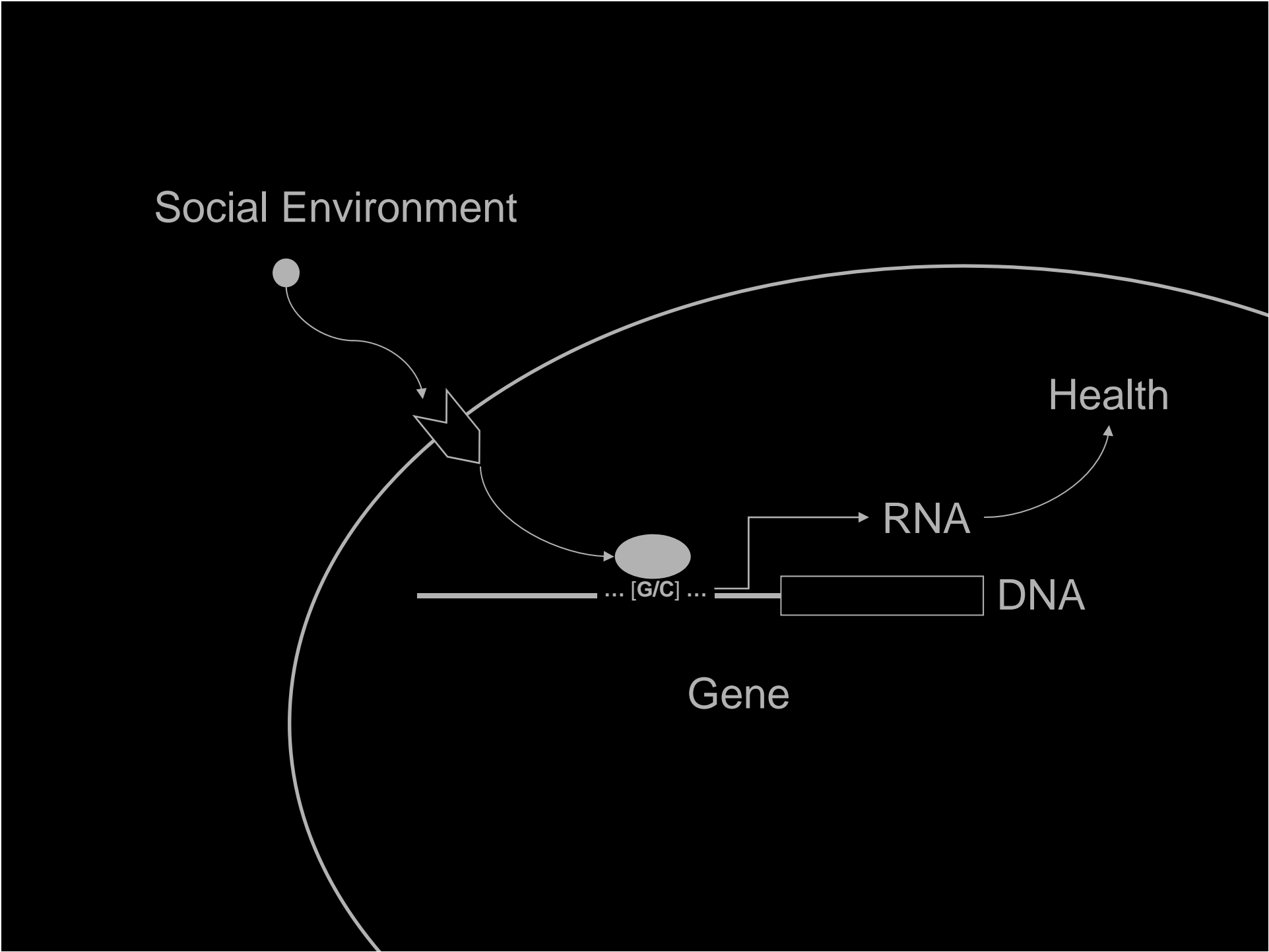
DNA

RNA

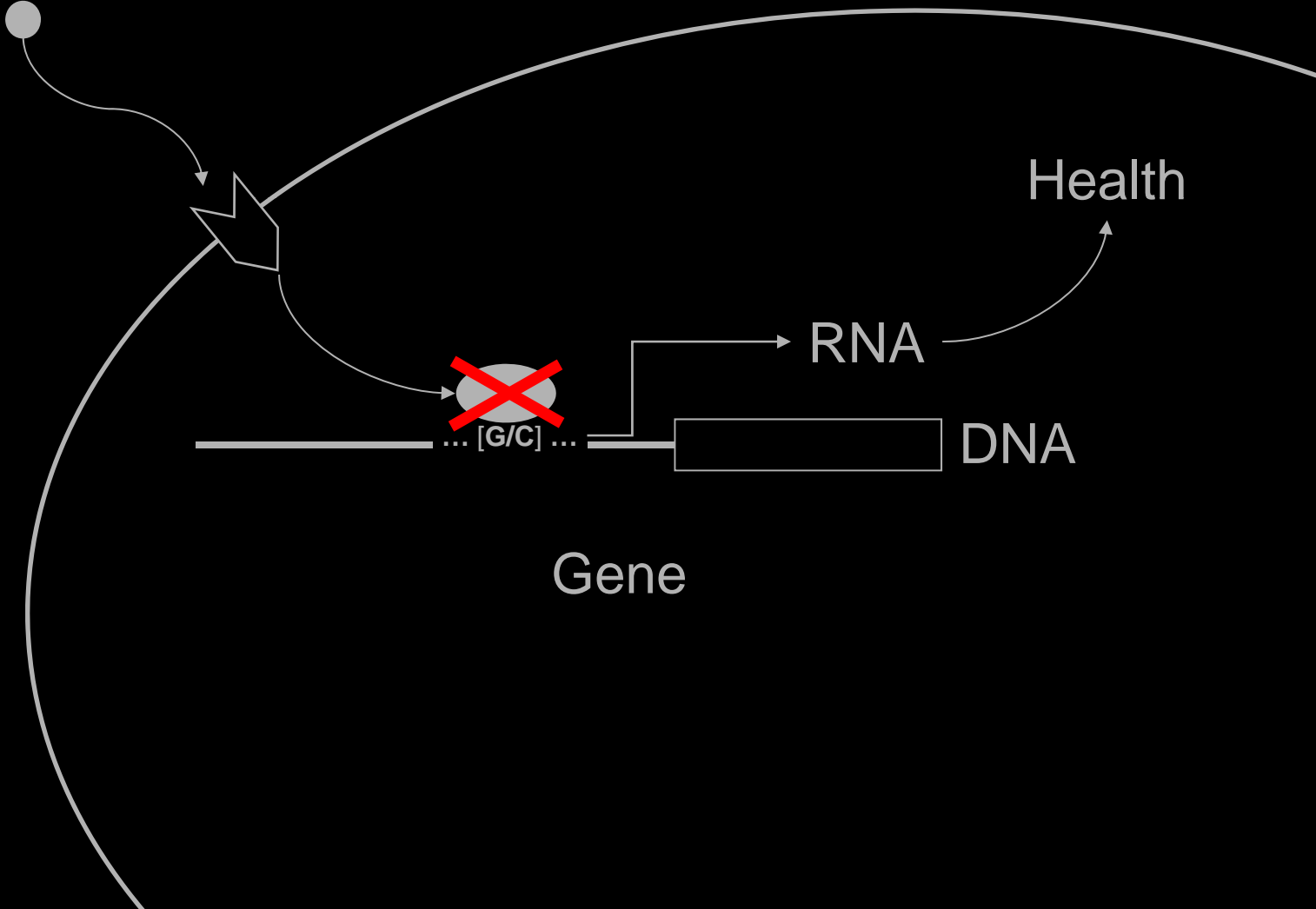
Health



Gene



Social Environment



Health

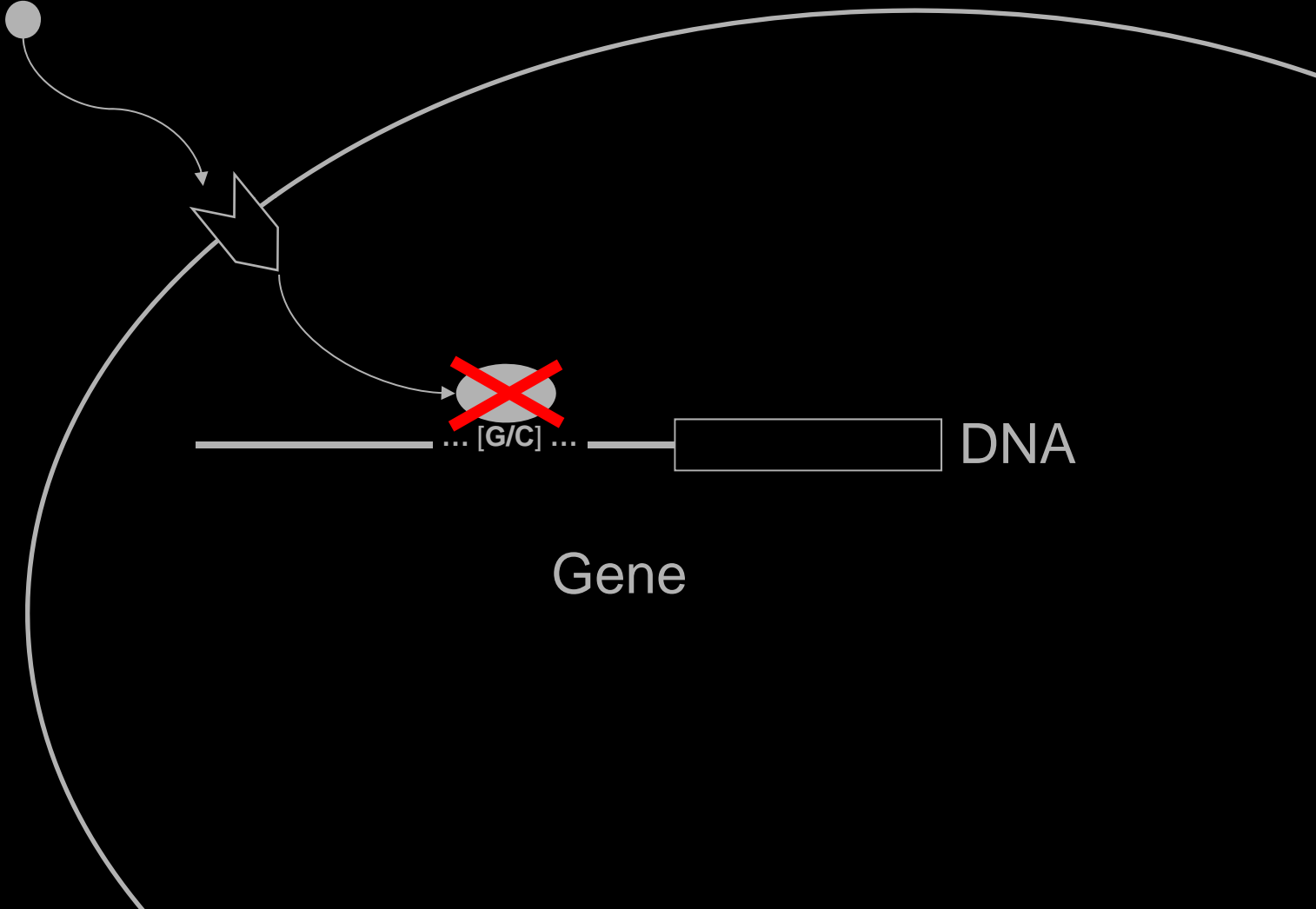
RNA

~~[G/C]~~

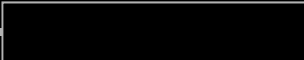
DNA

Gene

Social Environment



... [G/C] ...

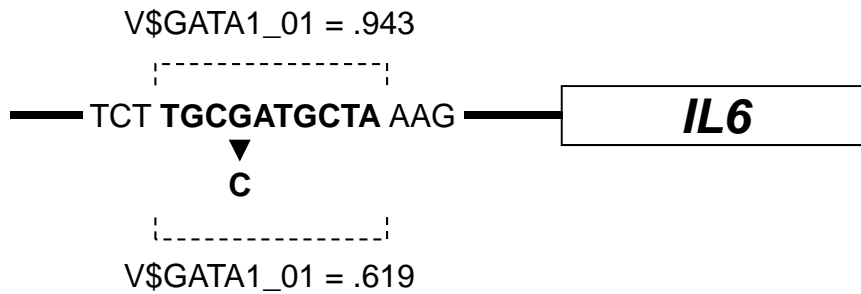


DNA

Gene

Gene x Environment Interaction

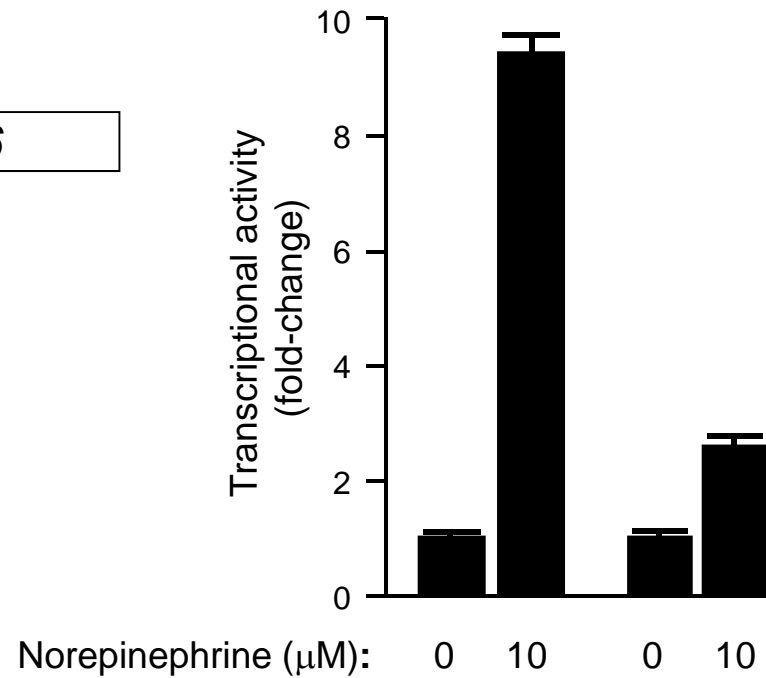
In silico



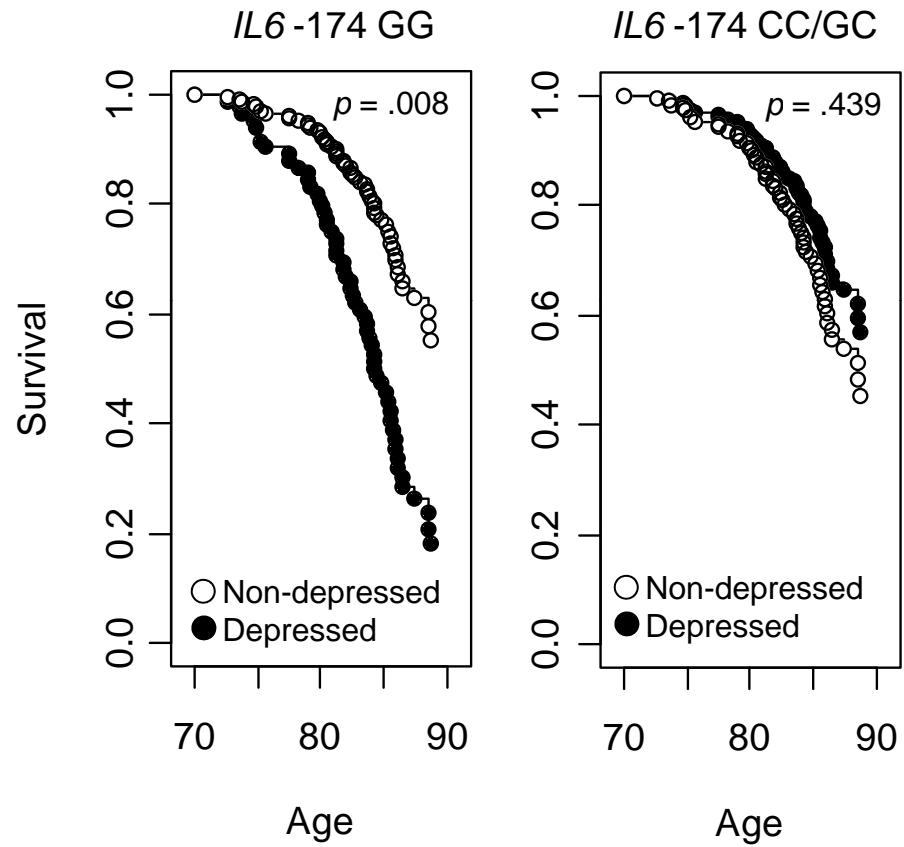
In vitro

IL6 promoter: WT -174C

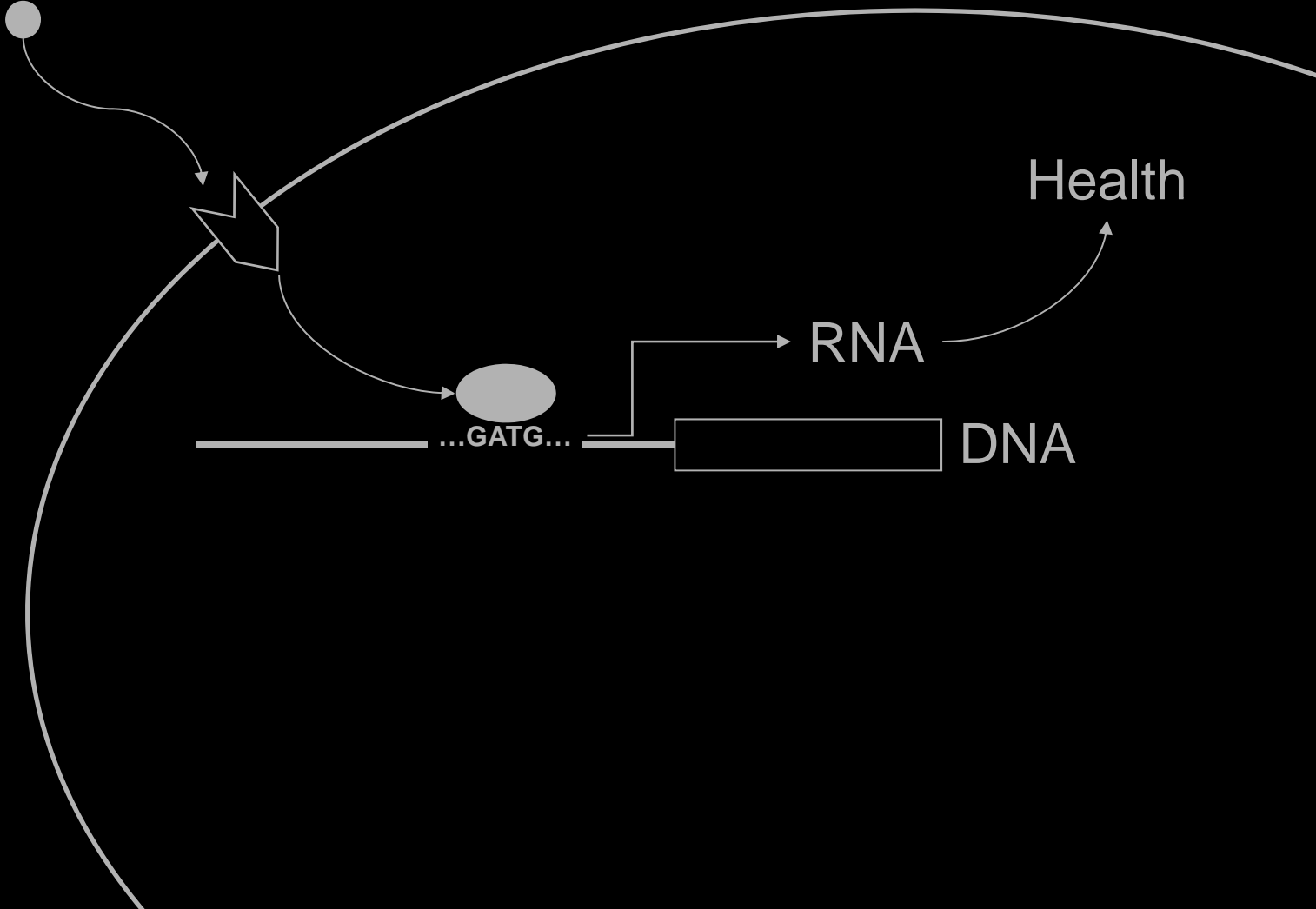
Difference: $p < .0001$



Gene x Environment Interaction

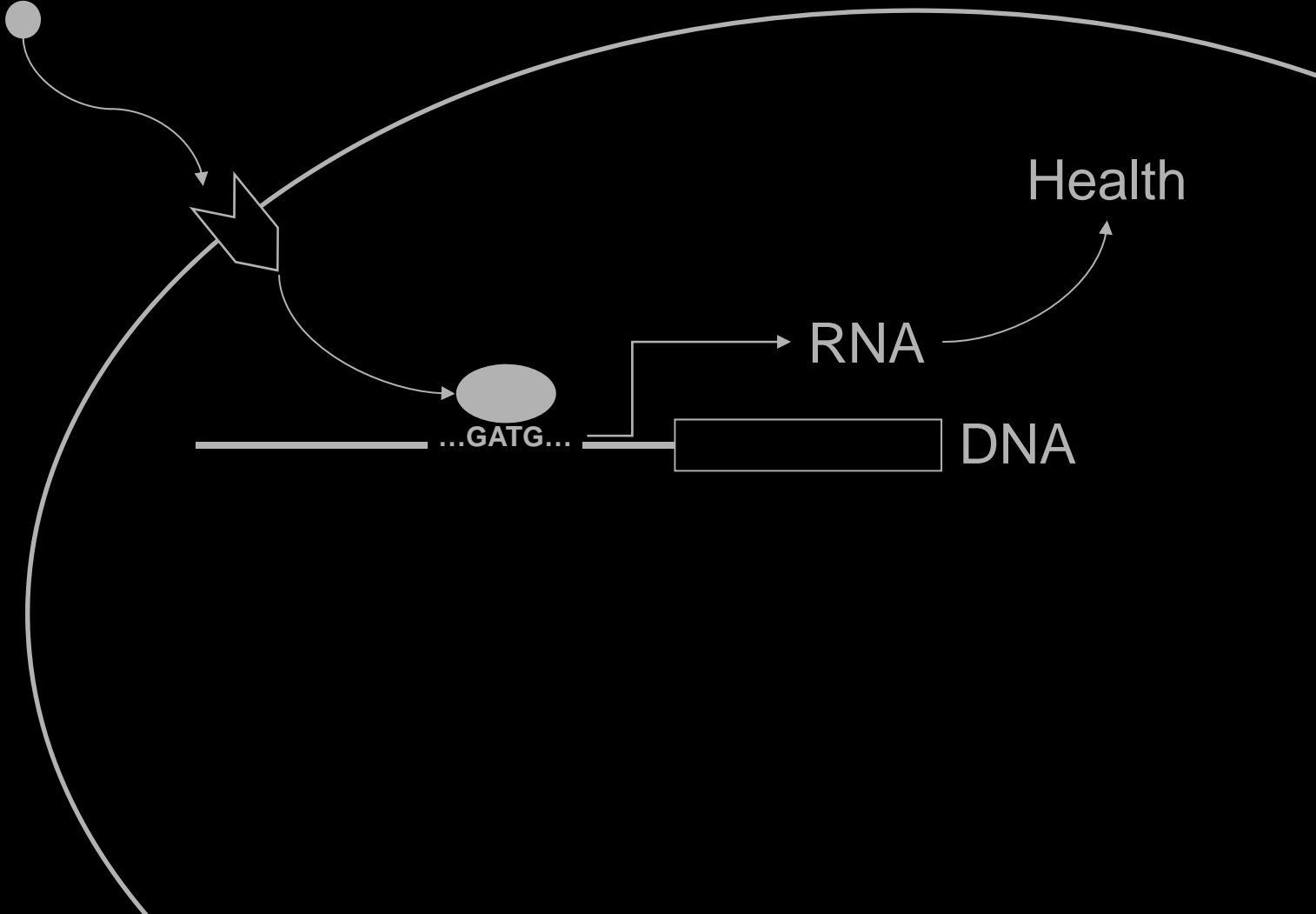


Social Environment



Adversity (depression)

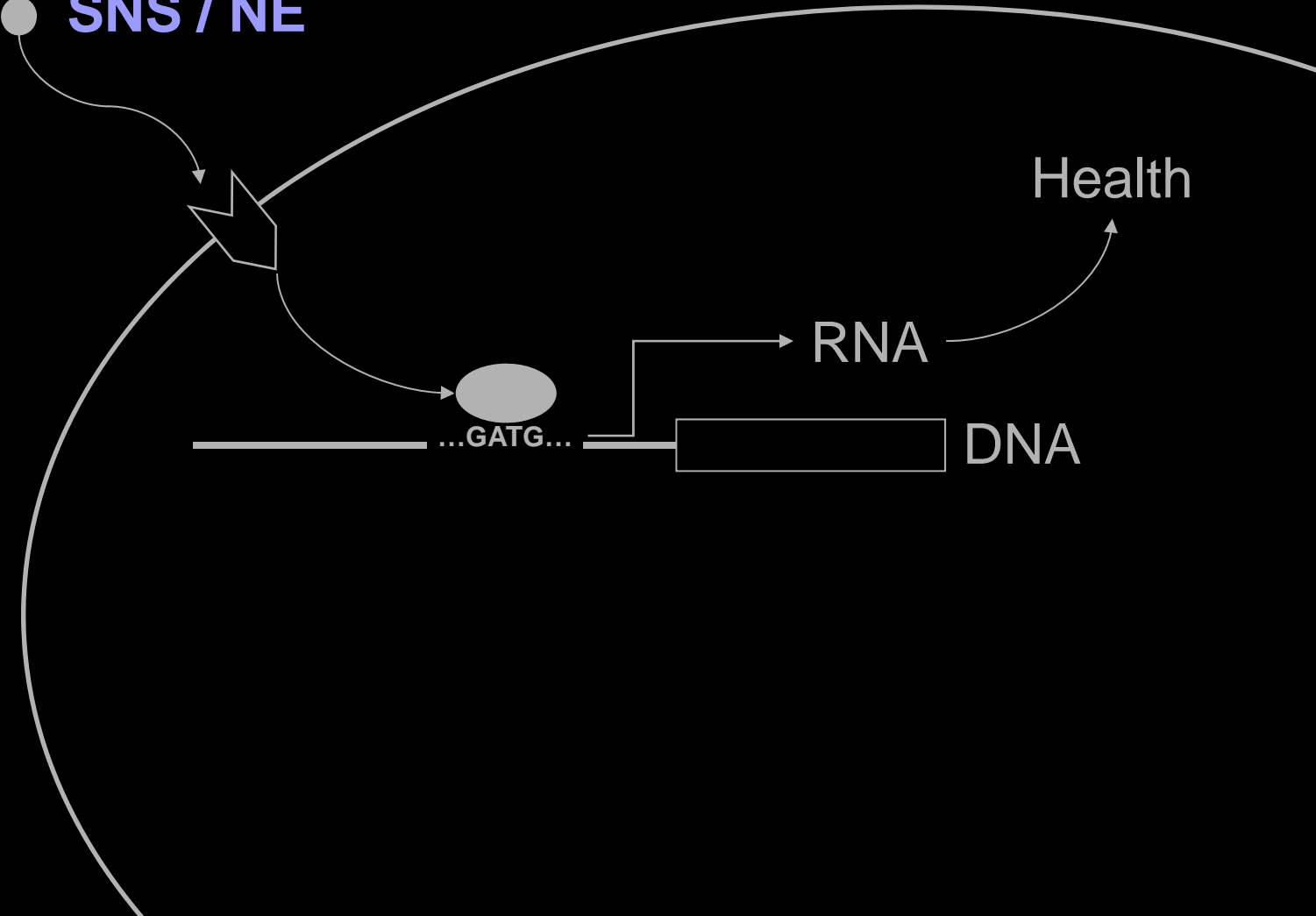
Social Environment



Adversity (depression)

Social Environment

● SNS / NE



Health

RNA

...GATG...

DNA

Adversity (depression)

Social Environment

● **SNS / NE**

β-AR

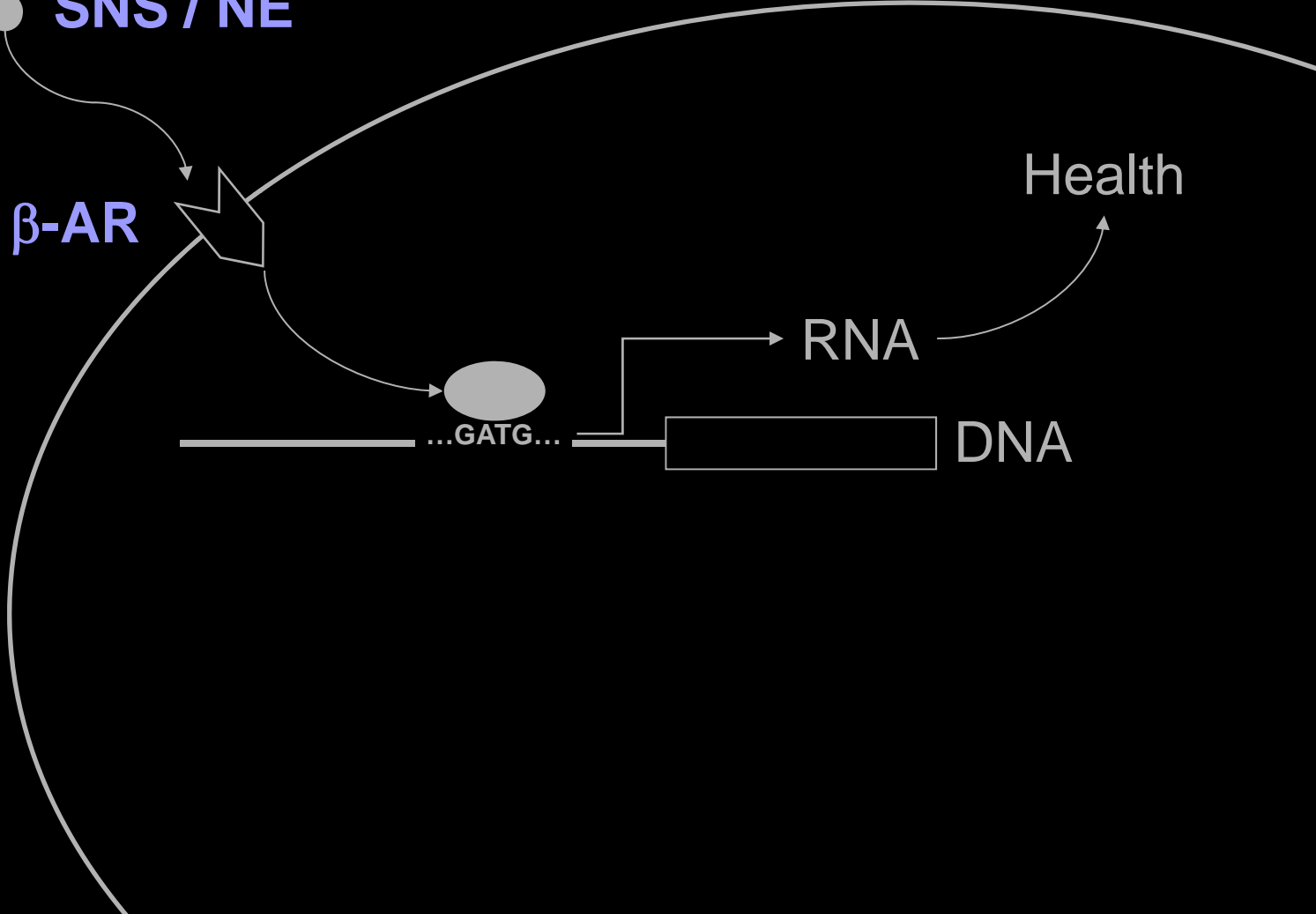
Health

RNA



...GATG...

DNA



Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1

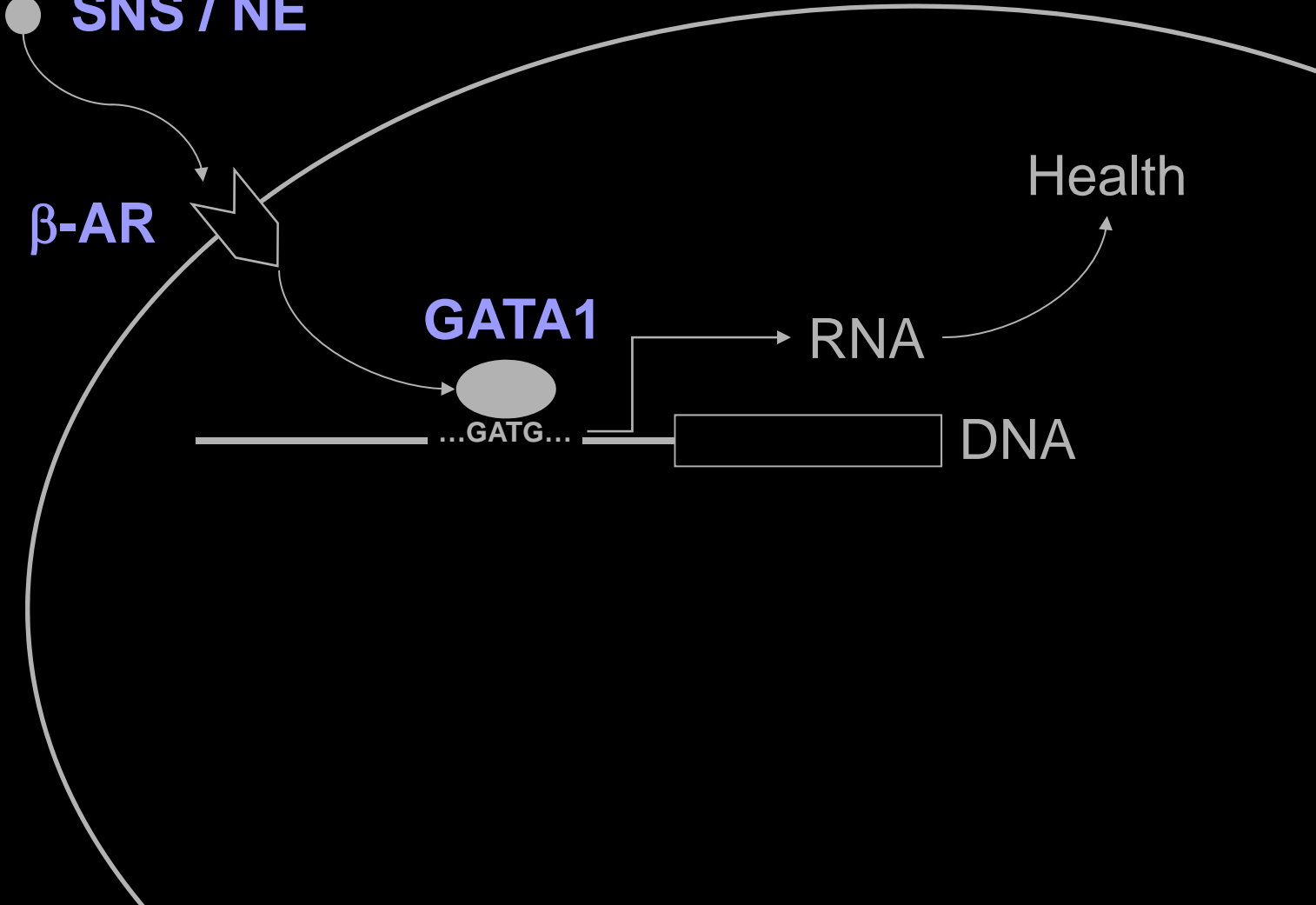


...GATG...

RNA

DNA

Health



Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1



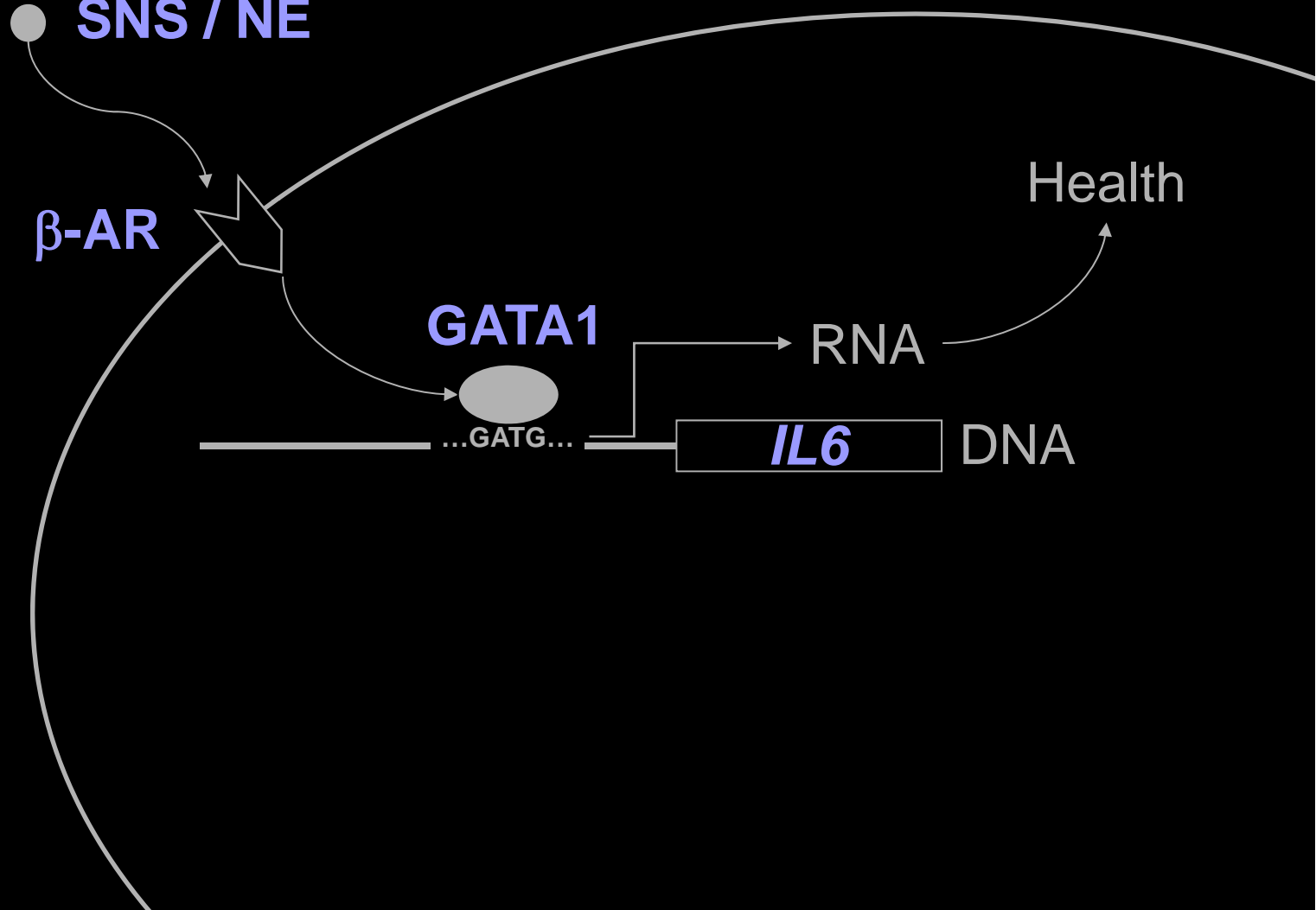
...GATG...

RNA

IL6

DNA

Health



Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1



...GATG...

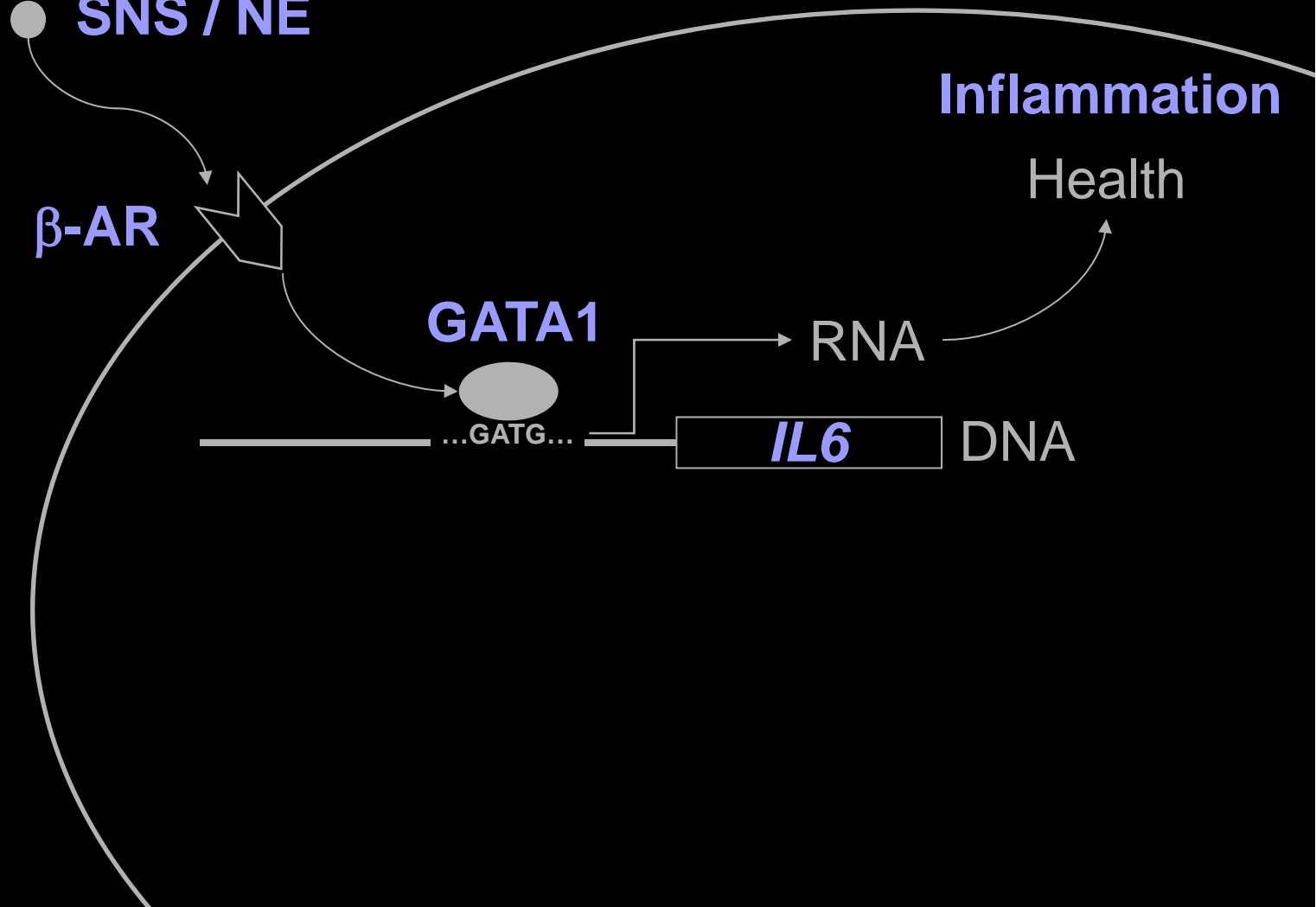
RNA

IL6

DNA

Inflammation

Health



Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1



...GATG...

RNA

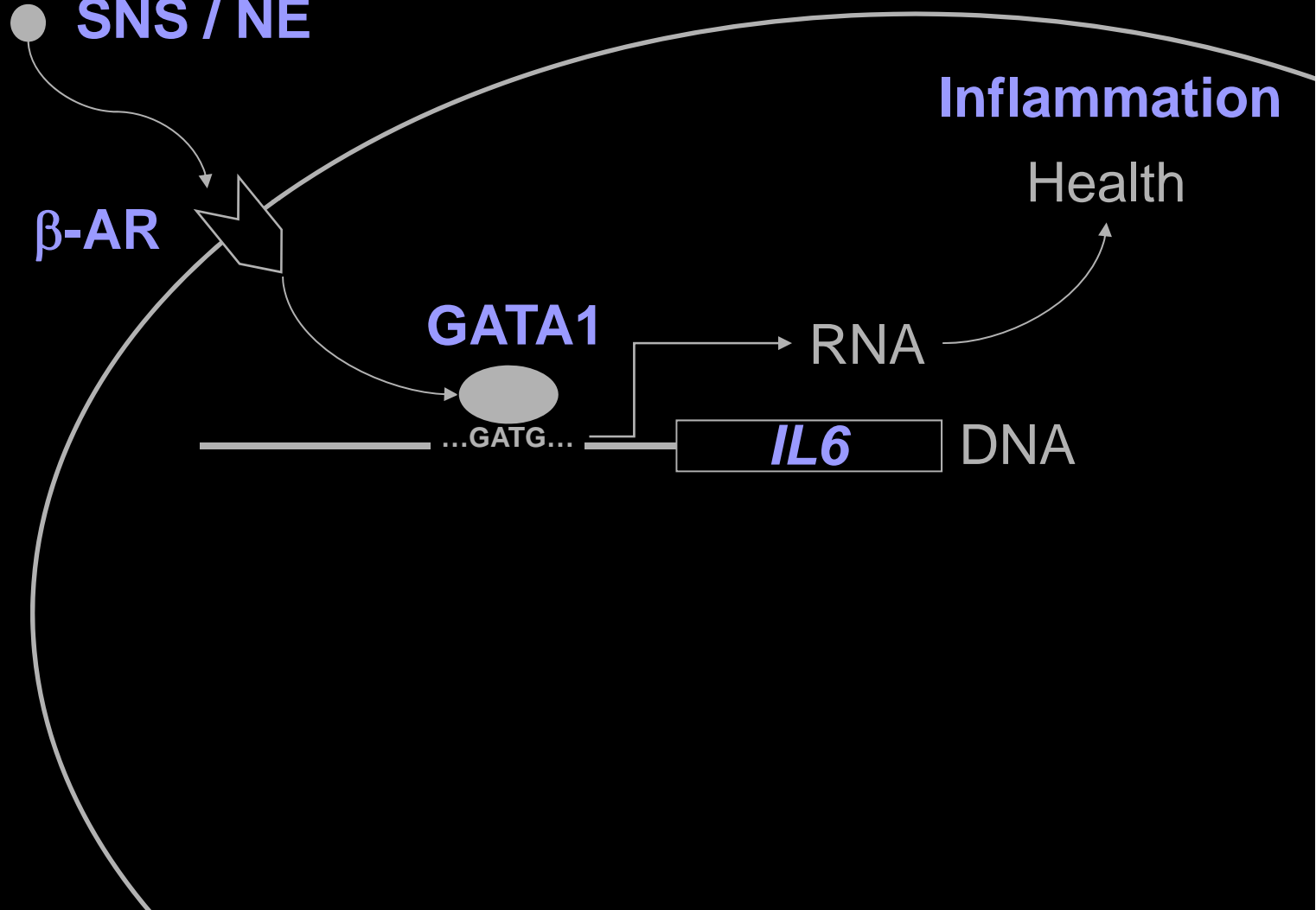
IL6

DNA

Mortality risk

Inflammation

Health



Adversity (depression)

Social Environment

Mortality risk

● SNS / NE

β -AR

Inflammation

Health

GATA1

RNA

...GATG...

IL6

DNA

rs1800795

Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1



...GATG...

rs1800795

RNA

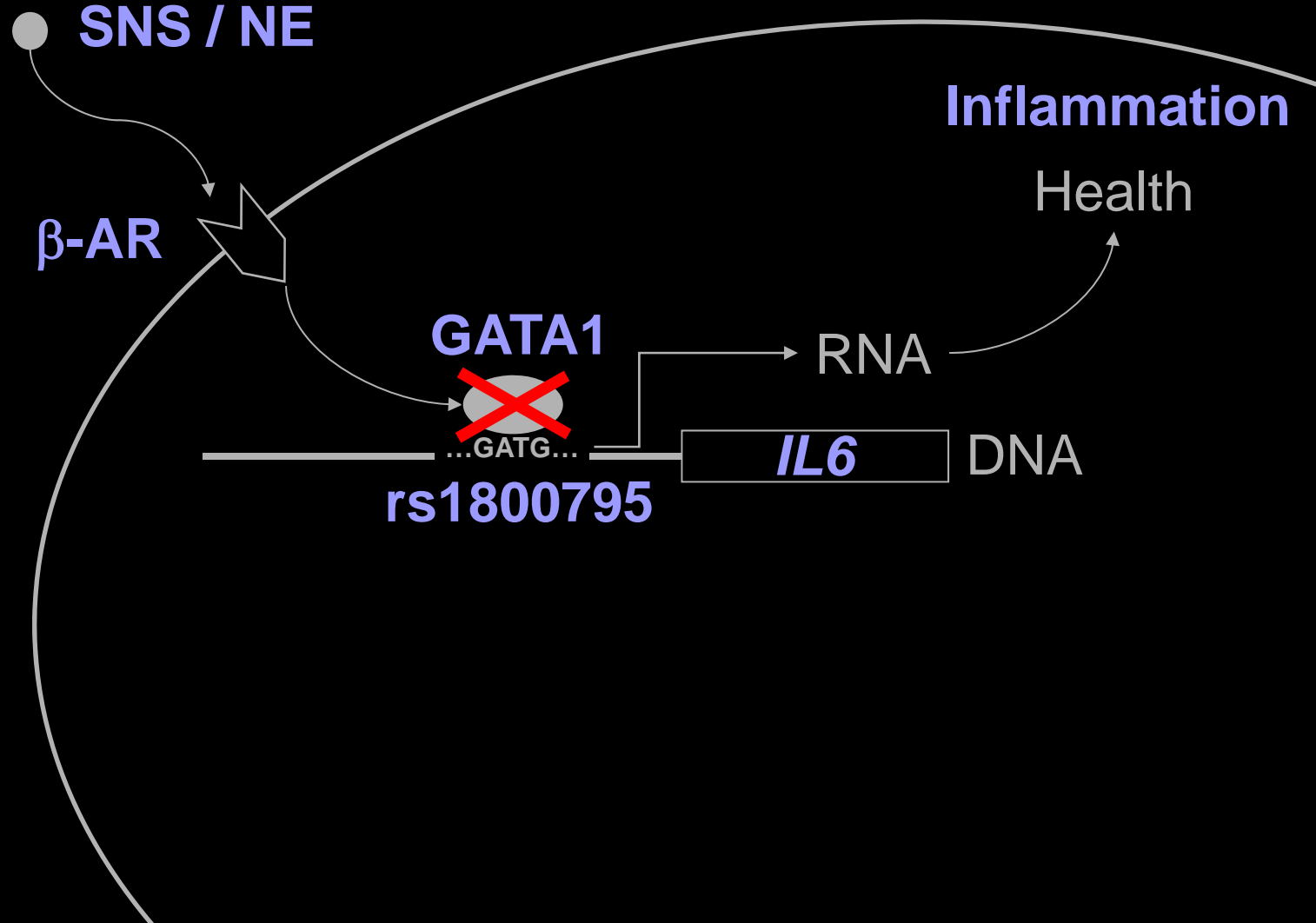
IL6

DNA

Mortality risk

Inflammation

Health



Adversity (depression)

Social Environment

● SNS / NE

β -AR

GATA1

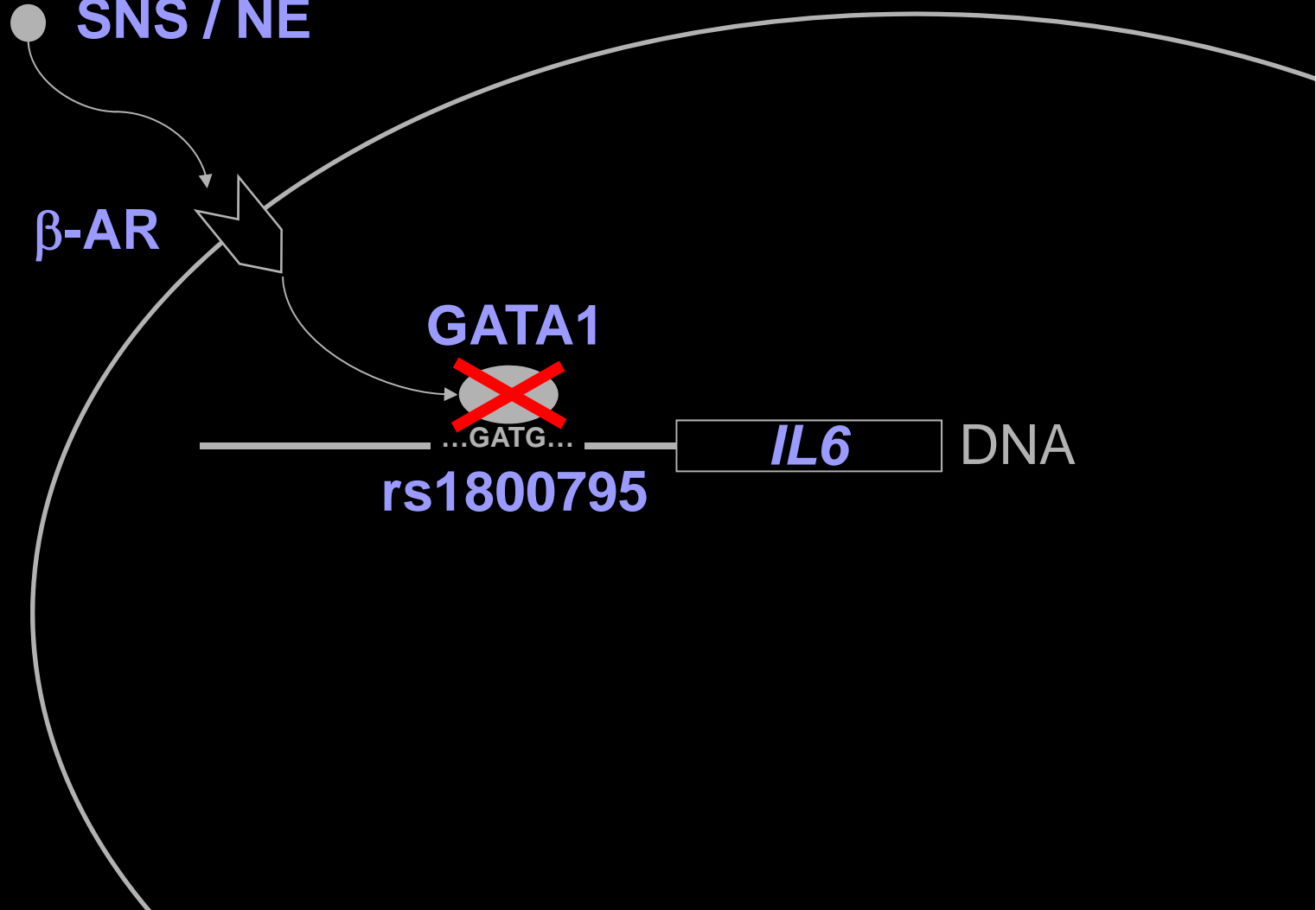


...GATG...

rs1800795

IL6

DNA



The experienced self

- stable
- independent

The experienced self

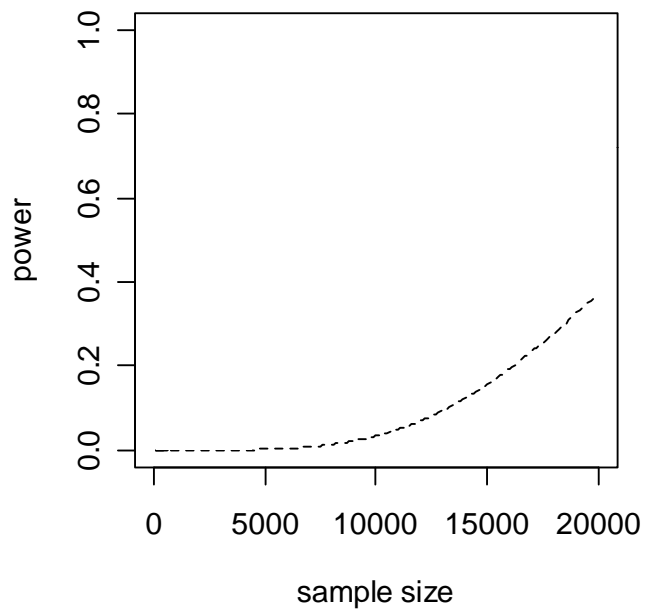
- stable
- independent

The molecular self

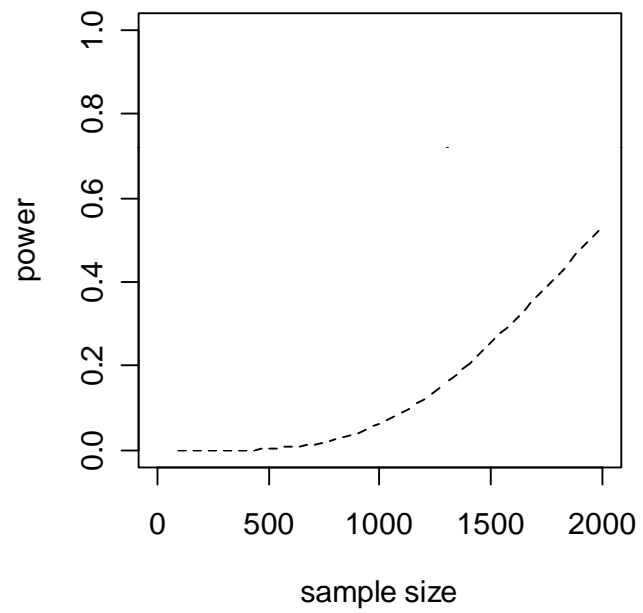
- fluid
- permeable

1200 GRE-modifying SNPs

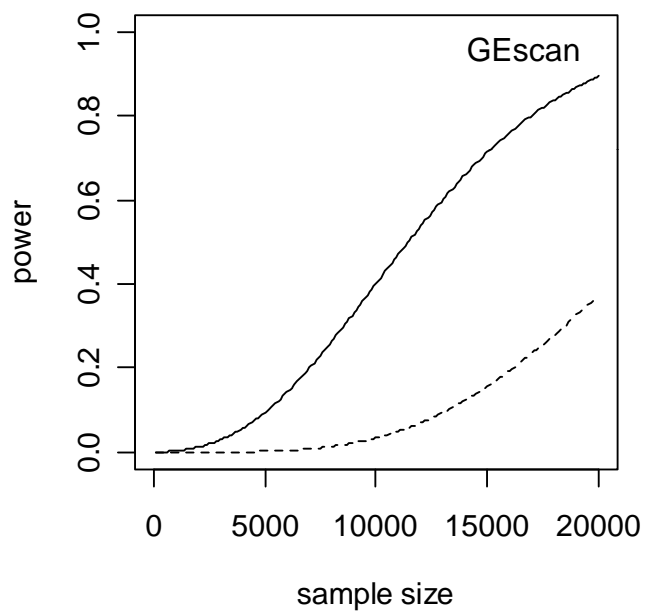
Population prevalence design



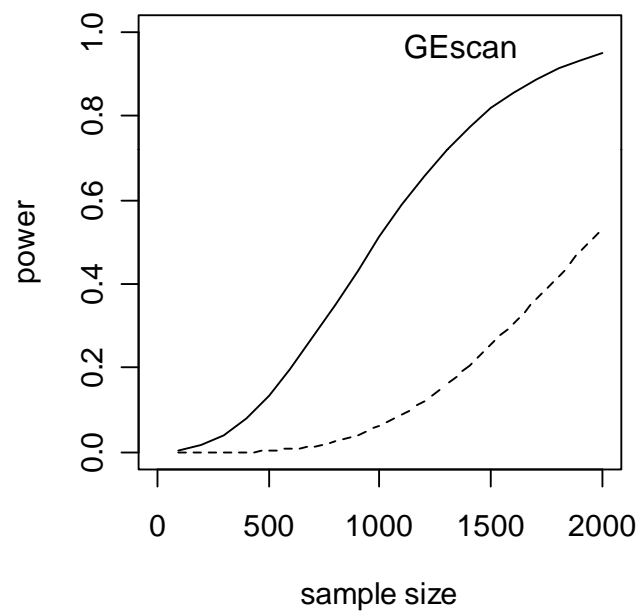
Outcome-stratified design



Population prevalence design



Outcome-stratified design



Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling

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Children reared in unfavorable socioeconomic circumstances show increased susceptibility to the chronic diseases of aging when they reach the fifth and sixth decades of life. One mechanistic hypothesis for this phenomenon suggests that social adversity in early life programs biological systems in a manner that persists across decades and thereby accentuates vulnerability to disease. Here we examine the basic tenets of this hypothesis by performing genome-wide transcriptional profiling in healthy adults who were either low or high in socioeconomic status (SES) in early life. Among subjects with low early-life SES, there was significant up-regulation of genes bearing response elements for the CREB/ATF family of transcription factors that conveys adrenergic signals to leukocytes, and significant down-regulation of genes with response elements for the glucocorticoid receptor, which regulates the secretion of cortisol and transduces its antiinflammatory actions in the immune system. Subjects from low-SES backgrounds also showed increased output of cortisol in daily life, heightened expression of transcripts bearing response elements for NF- κ B, and greater stimulated production of the proinflammatory cytokine interleukin 6. These disparities were independent of subjects' current SES, lifestyle practices, and perceived stress. Collectively, these data suggest that low early-life SES programs a defensive phenotype characterized by resistance to glucocorticoid signaling, which in turn facilitates exaggerated adrenocortical and inflammatory responses. Although these response patterns could serve adaptive functions during acute threats to well-being, over the long term they might exact an allostatic toll on the body that ultimately contributes to the chronic diseases of aging.

nurturance or experience prolonged maternal separations can show permanent alterations in stress-related outflow of the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenocortical (HPA) axis (8–10). These effects are partially mediated by diminished expression of and signaling by the glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates HPA outflow through a hippocampal negative-feedback circuit (11, 12). The effects of early social adversity also extend to the immune system (13). For example, mice that are repeatedly separated from their mothers early in life show an excessive inflammatory response and reduced viral clearance after influenza infection in adulthood (14), an effect that is partially mediated by impaired glucocorticoid regulation of cytokine release.

Collectively, these data suggest that repeated social adversity in early life can program a “defensive” phenotype, which is marked by exaggerated adrenocortical and inflammatory responses to challenge (15). Some evidence indicates that this phenotype involves the development of a functional resistance to GR-mediated signaling, which allows cortisol to partially escape inhibition by negative feedback and facilitates the synthesis of proinflammatory mediators by leukocytes. In social contexts where threats like crowding, predation, and conflict are common, these response patterns might confer a survival advantage by helping organisms to rapidly mobilize energy for fighting and fleeing and to mount vigorous immune responses to infection and injury (15). However, in the context of late-life chronic illnesses, dysregulated GR signaling may enable exaggerated inflammatory responses that contribute to the pathogenesis of cardiovascular disease, some types of cancer, and respiratory conditions.

cortisol | inflammation | NF-kappa B | socioeconomic status | stress