CoT Trajectories

10/31/2025

Objective:

Make each CoT’s embedding path look continuous

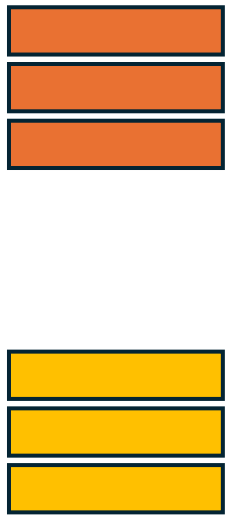
in order to diagnose discontinuities with minimal experiments.

Methods

```
[STEP 1] Map Targets → Pathways/Processes

*   **Abiraterone:**
    *   **Targets:** CYP17A1.
    *   **Pathways/Processes:** Androgen Receptor (AR) Signaling (primary
inhibition of androgen synthesis, upstream of AR activation), Steroidogenesis.
    *   **Relationship:** Serial bottleneck (blocks androgen precursor
synthesis, which is essential for AR signaling). Inhibition of CYP17A1 leads
to downstream reduction of AR activity.
```

- Split into segments
  - Period (sentence)
  - ** (bold headings) -- includes whitespace \n\n
- Combine
  - 3, 5 segments
- Overlap
  - 0, 1 segments



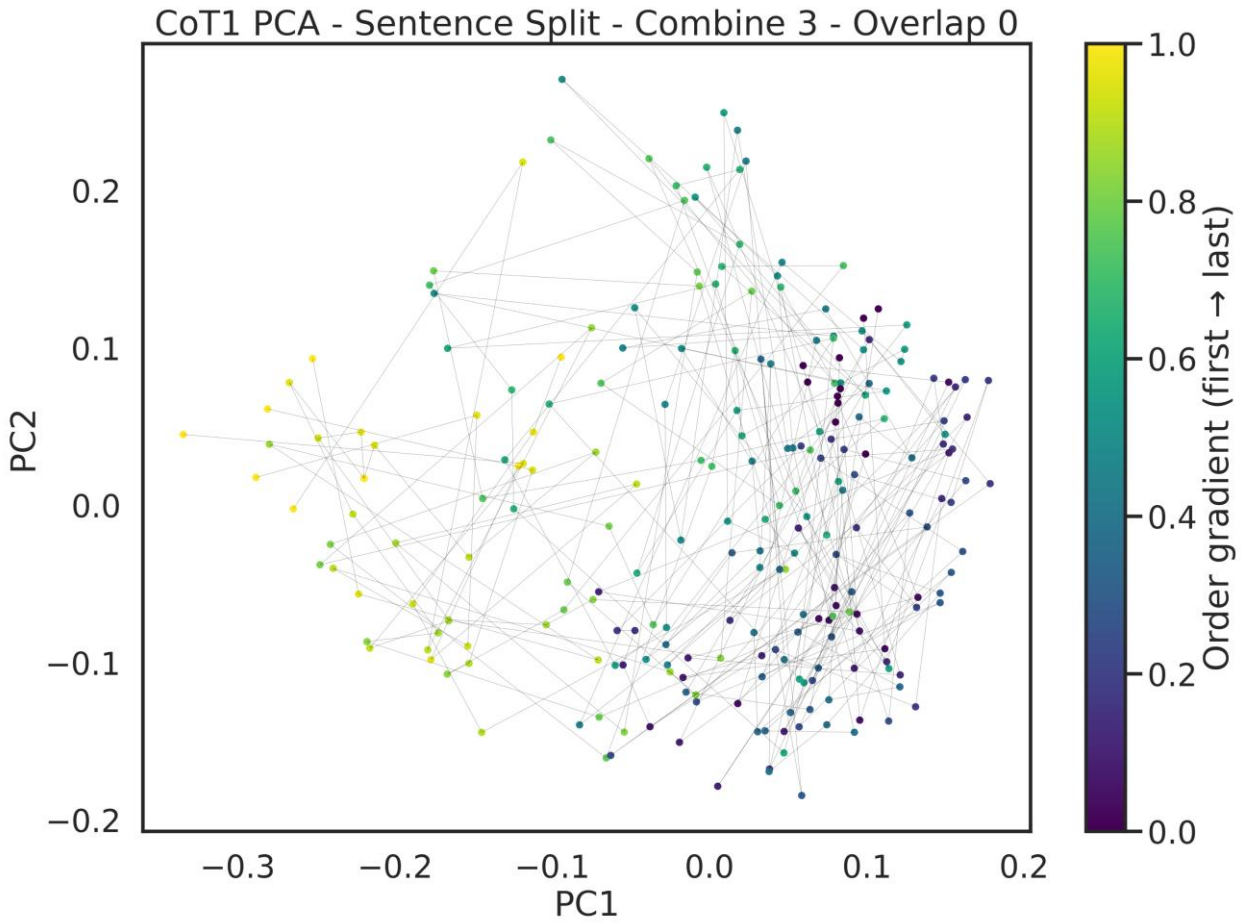
Combine 3, overlap 0

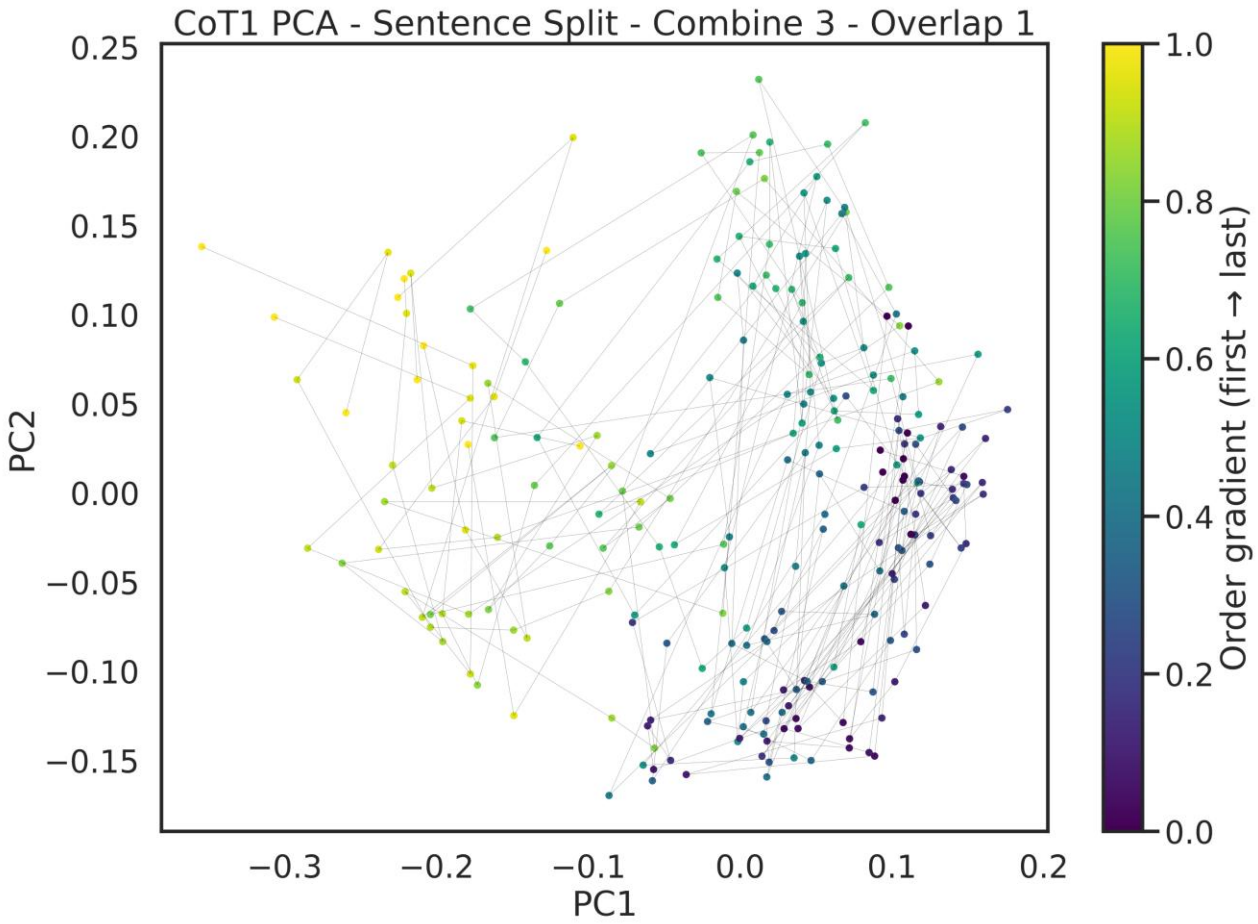
Combine 3, overlap 1

CoT1

More structured than CoT2

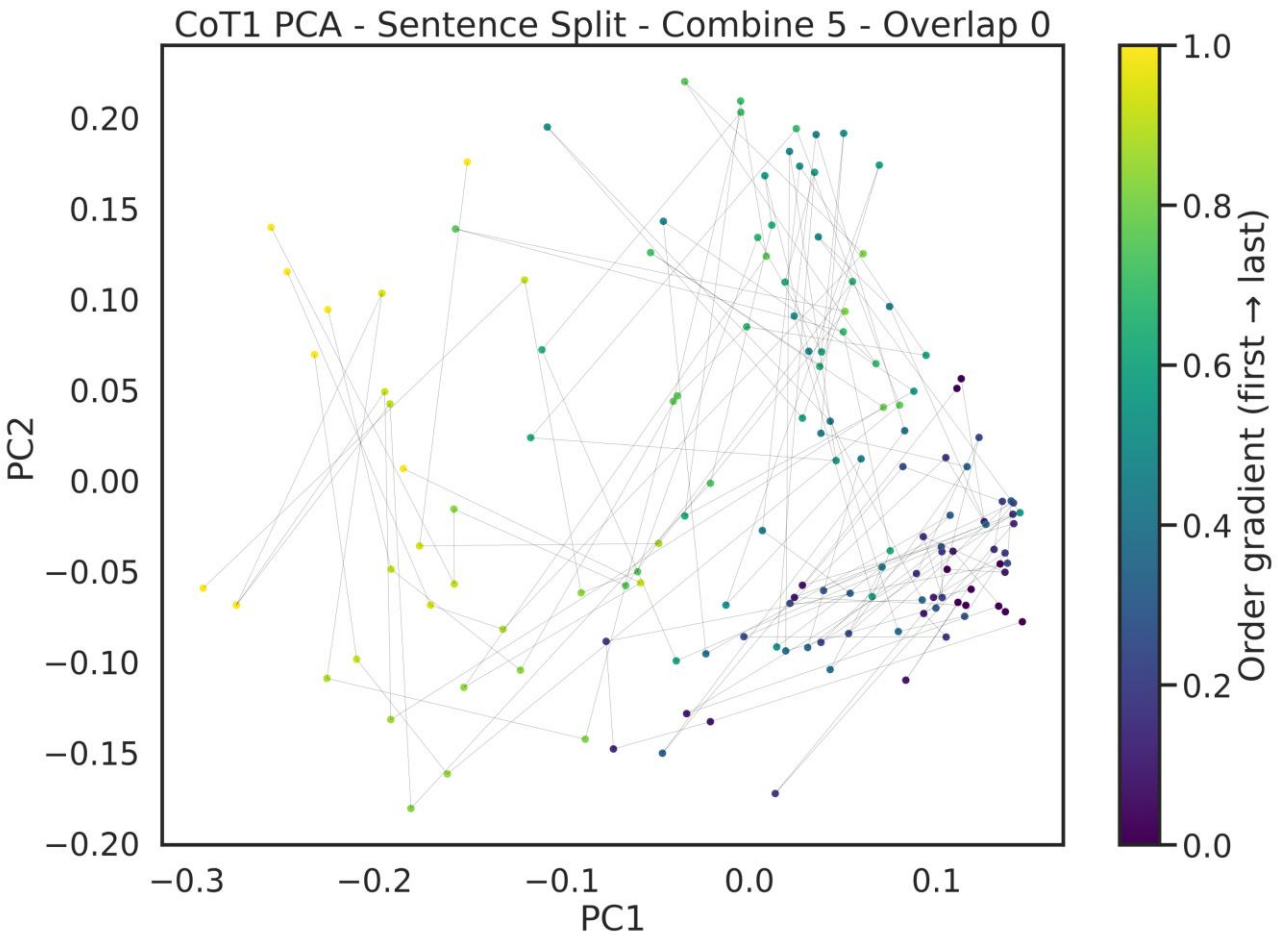
CoT1, Sentence Split, Combine 3

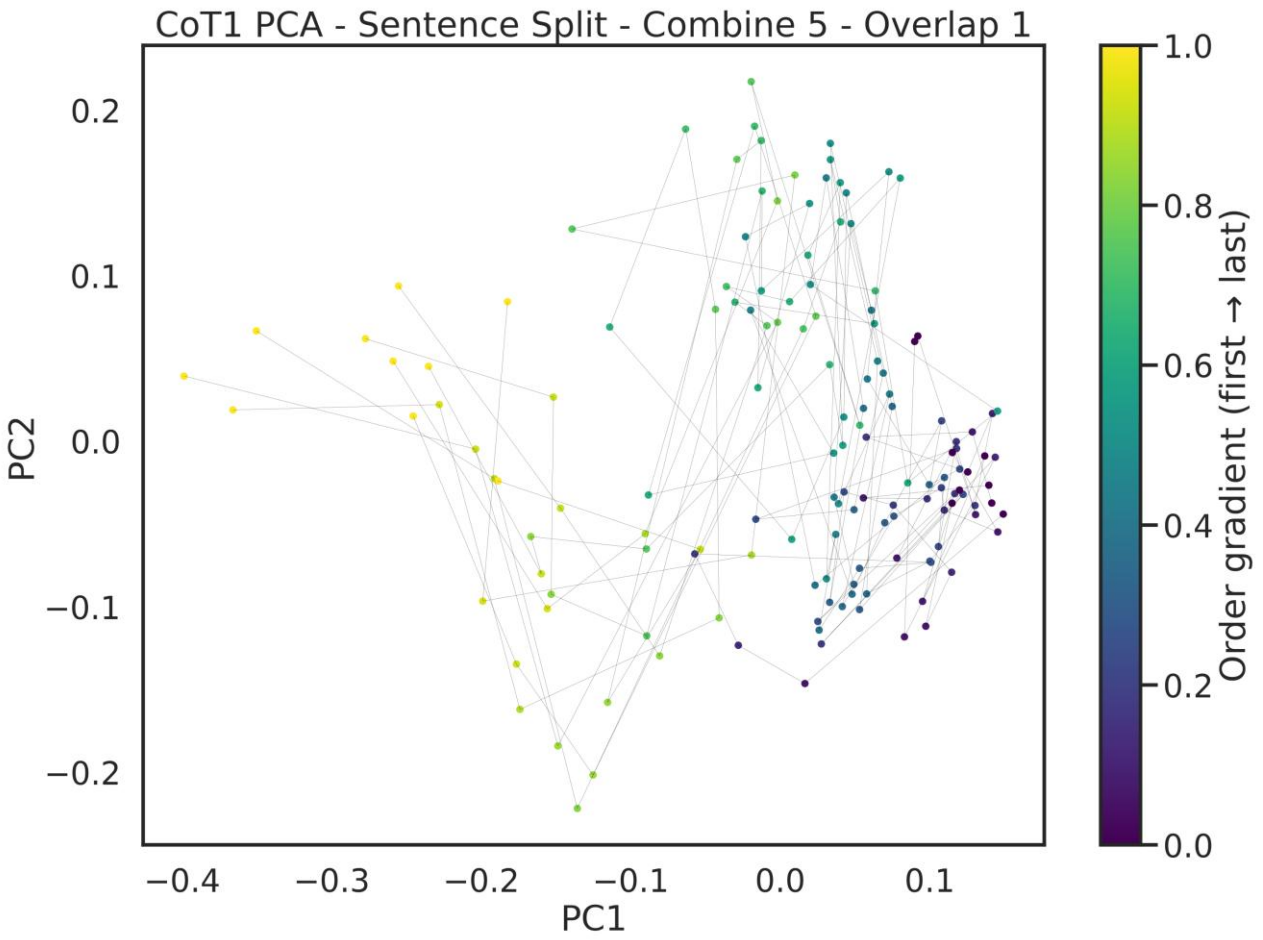




Having overlap -> more separation

CoT1, Sentence Split, Combine 5

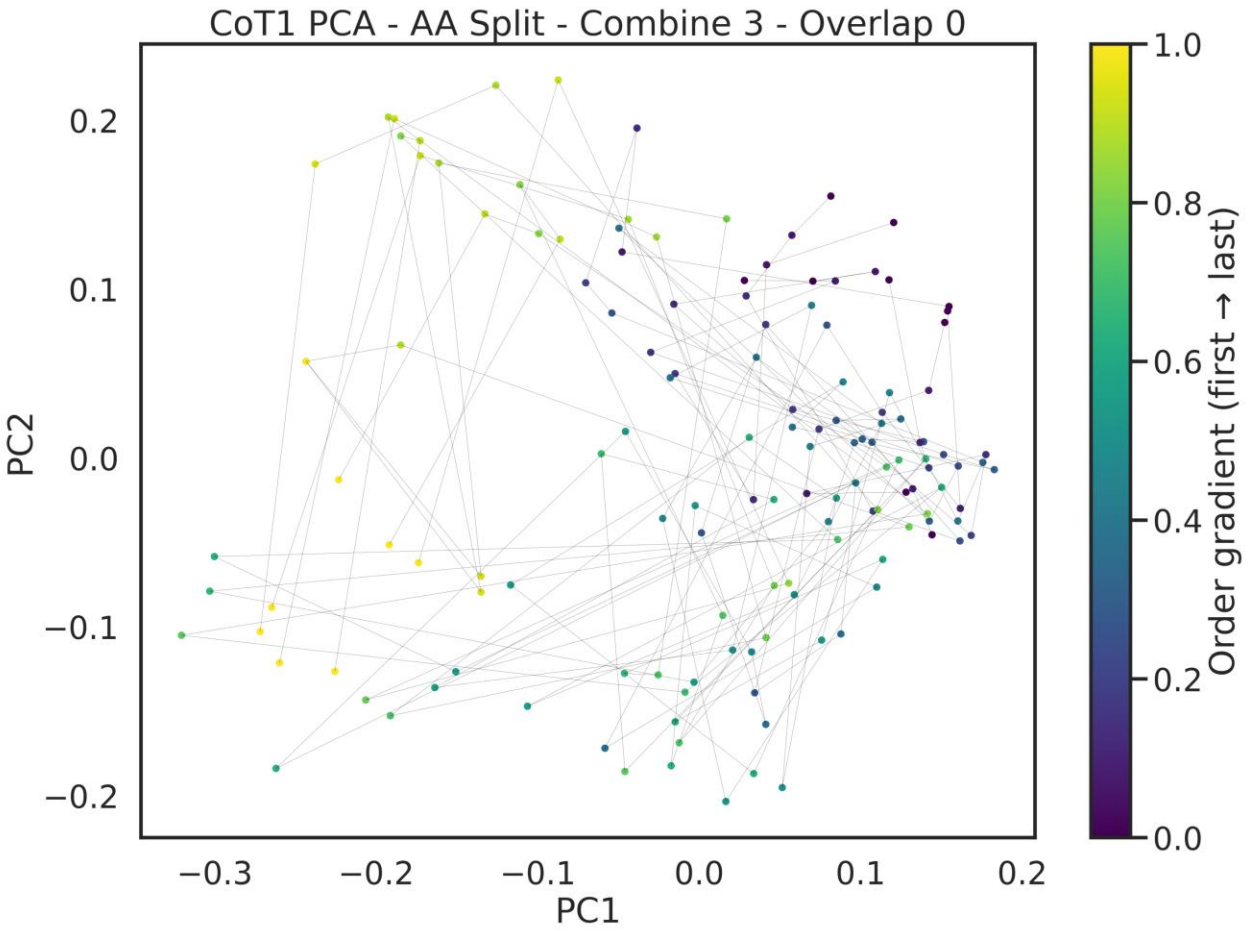


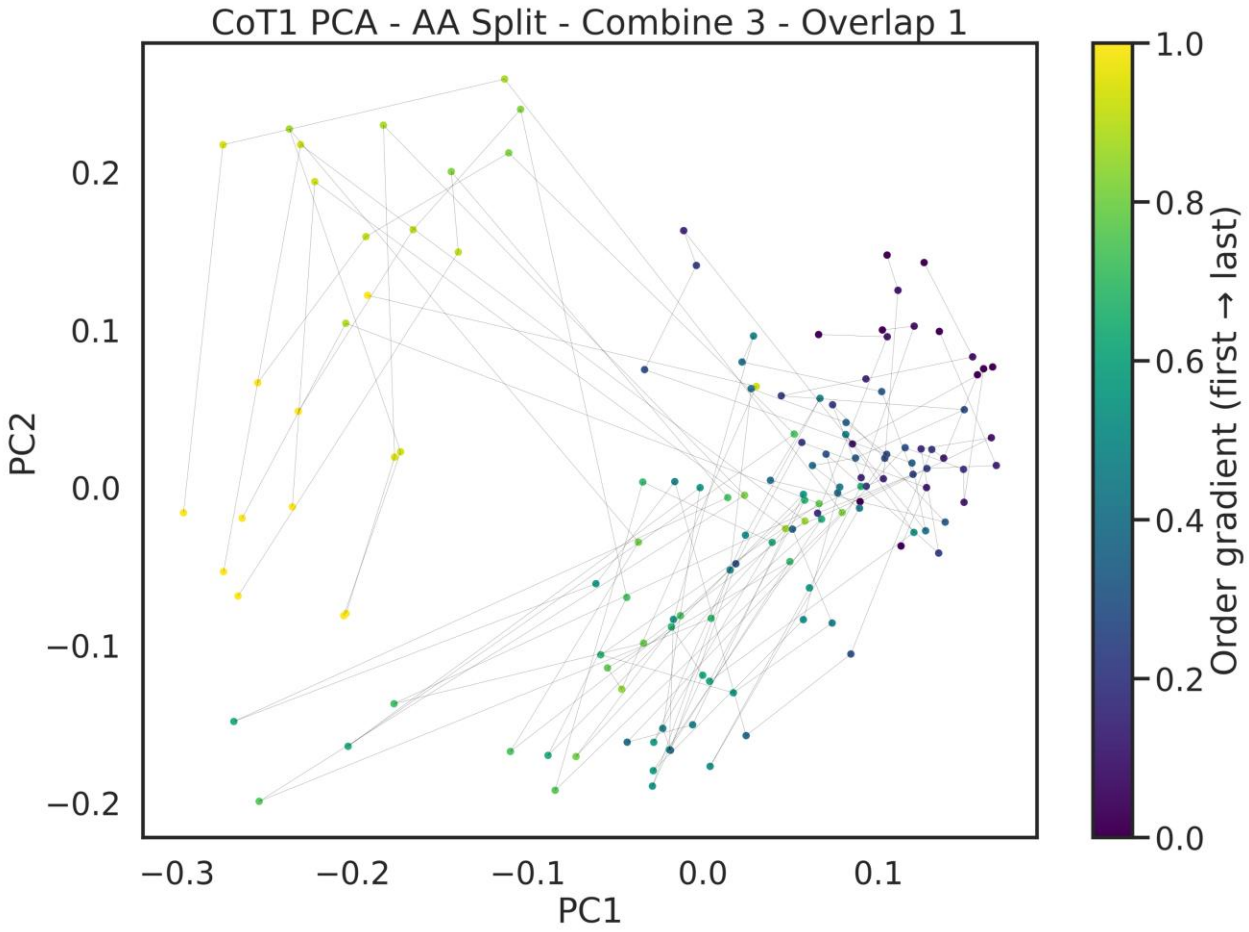


Combine 5 has clearer trajectory than combine 3

Having overlap -> more separation-> stabilization

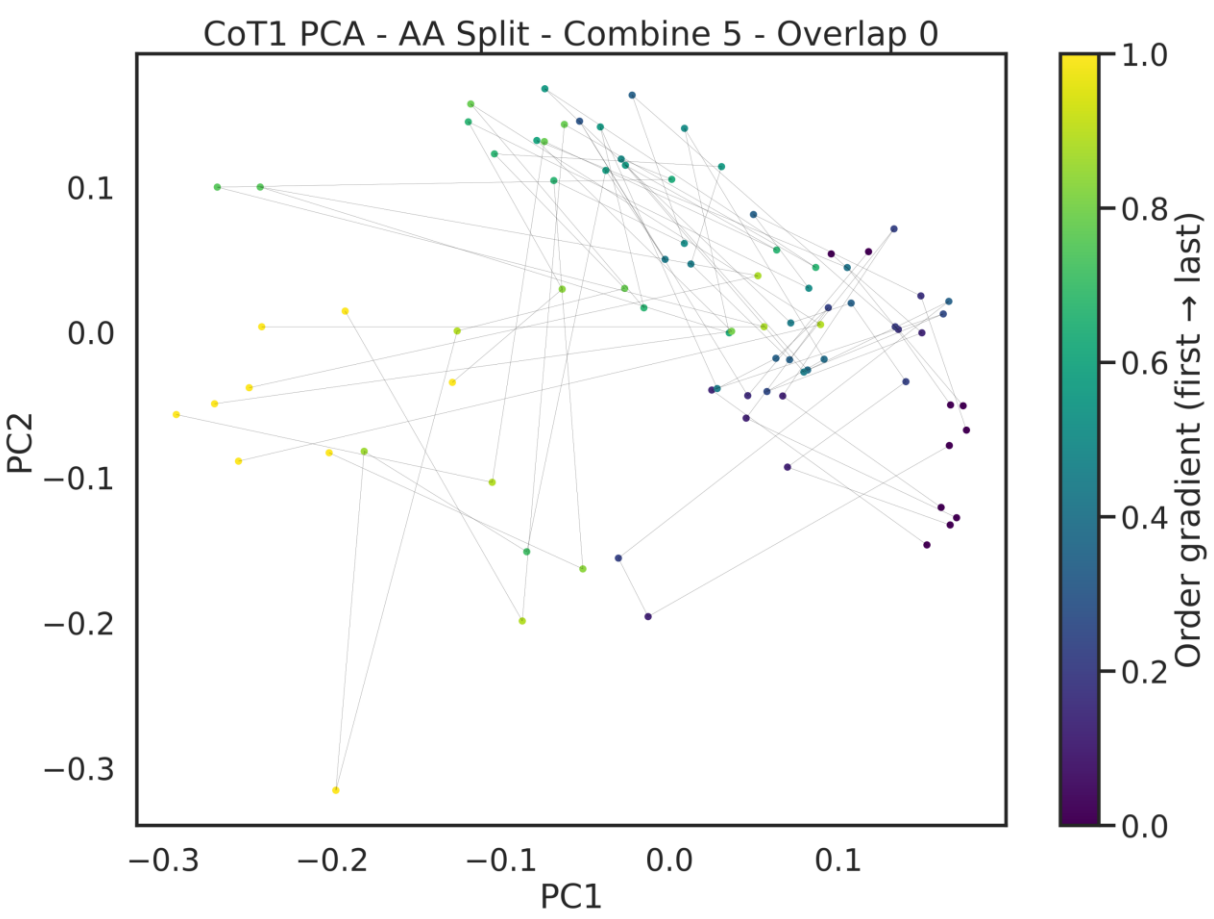
CoT1, Bold Split, Combine 3

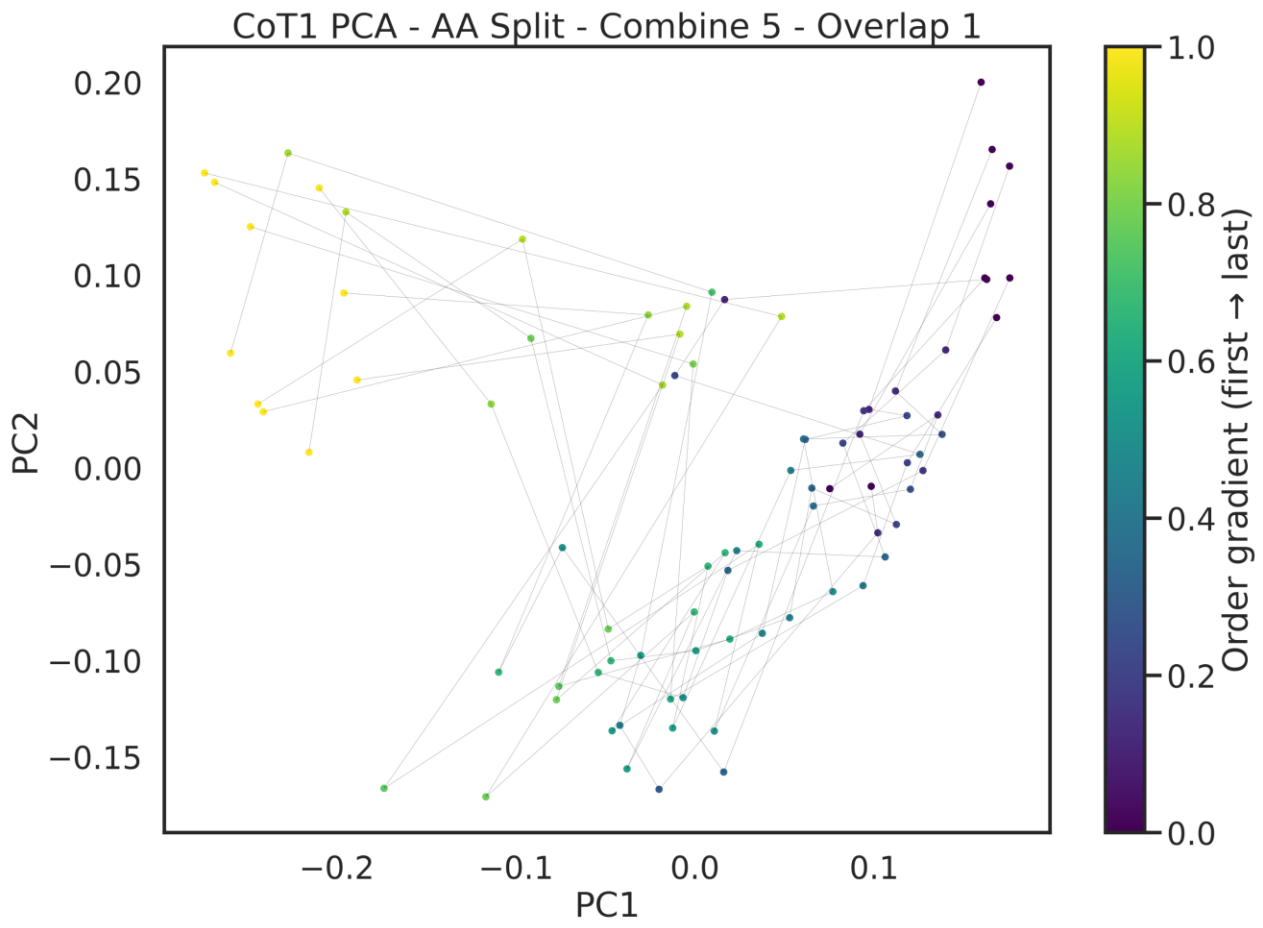




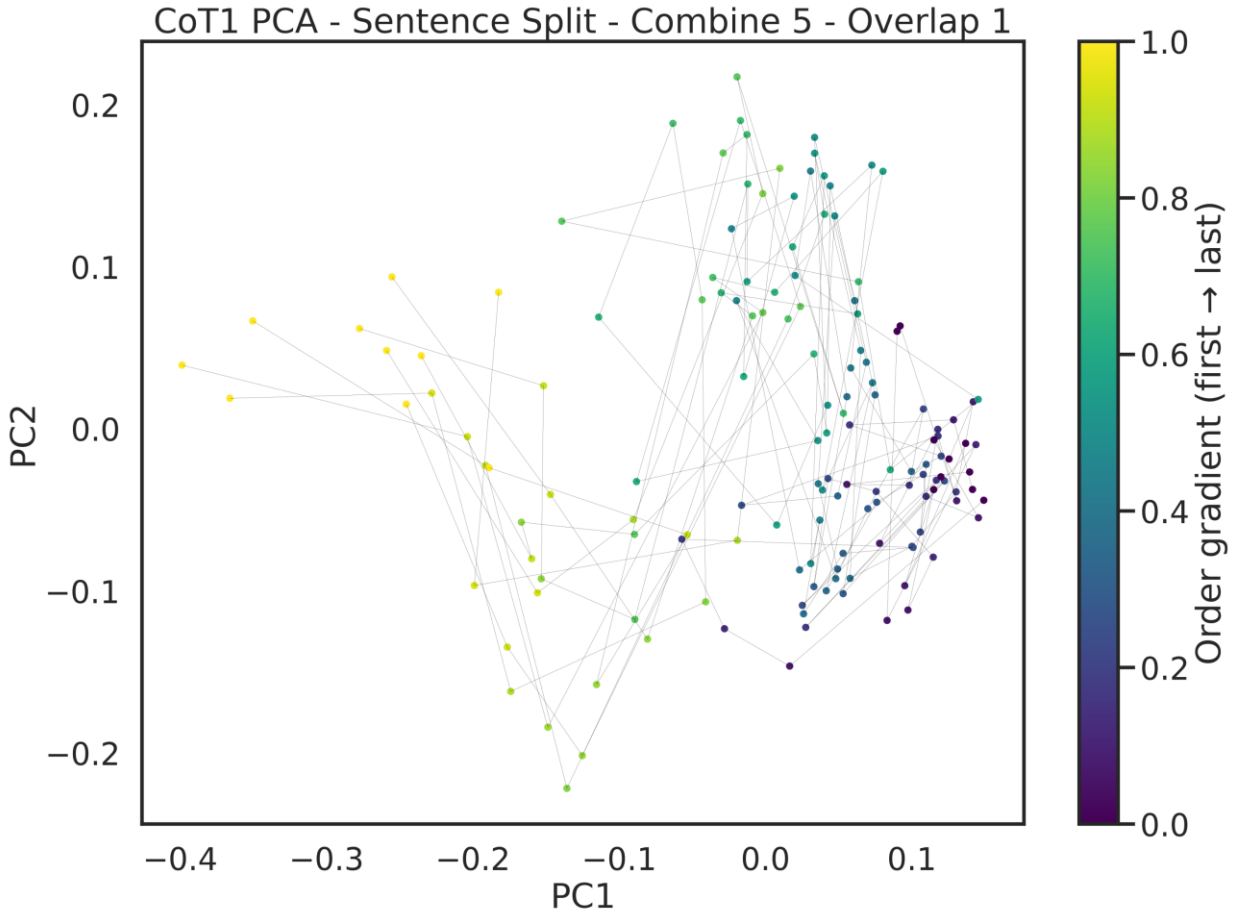
Having overlap -> stabilization effect

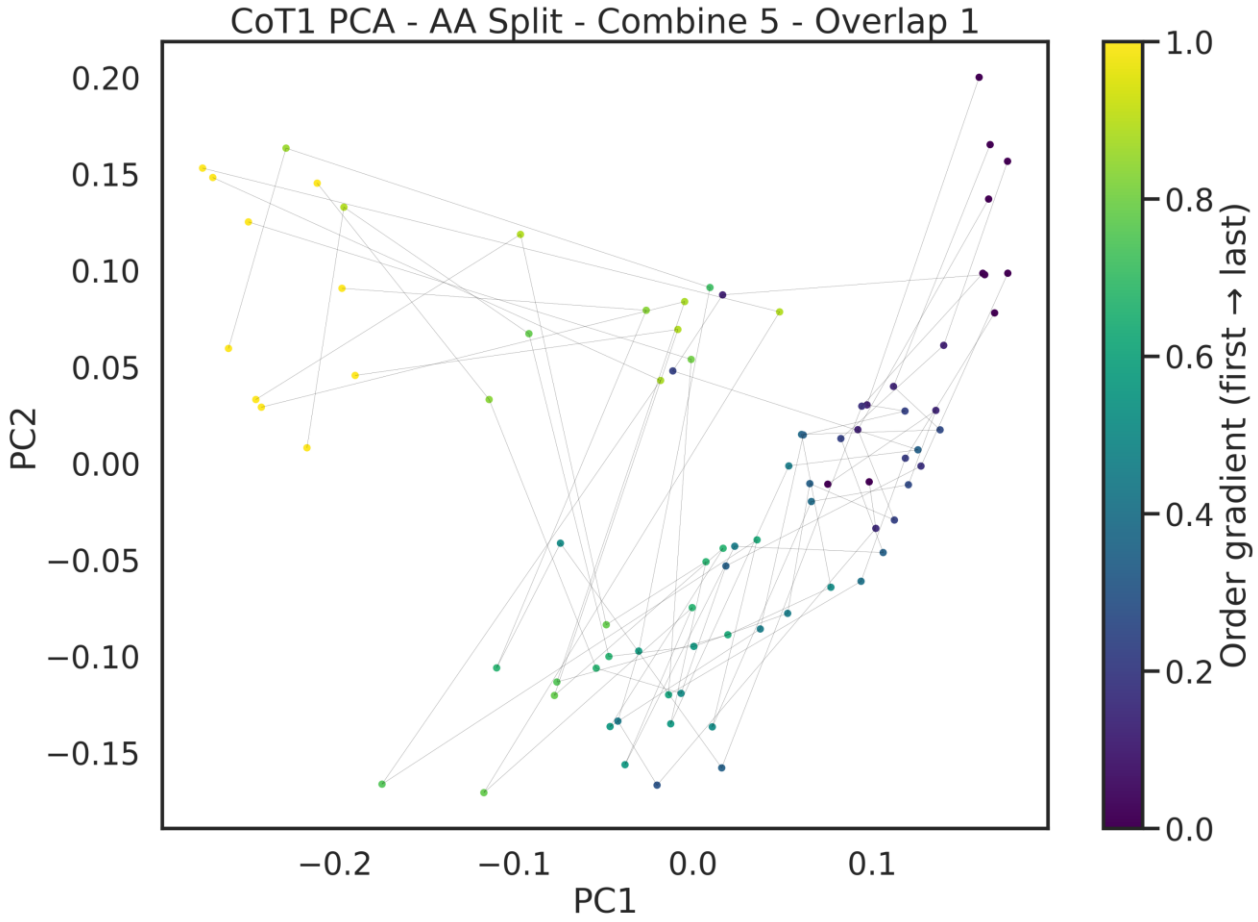
CoT1, Bold Split, Combine 5





CoT1 Split: Sentence vs Bold



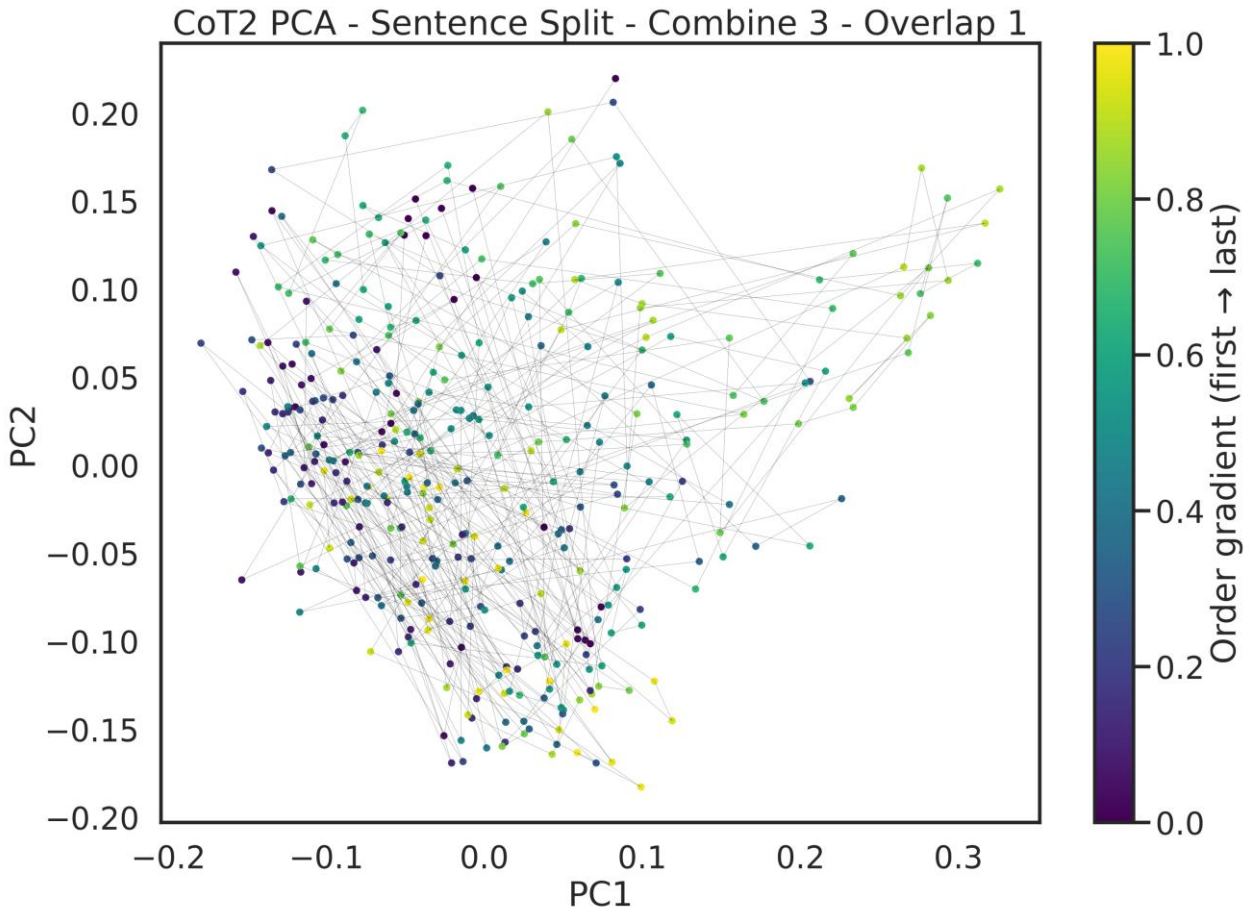


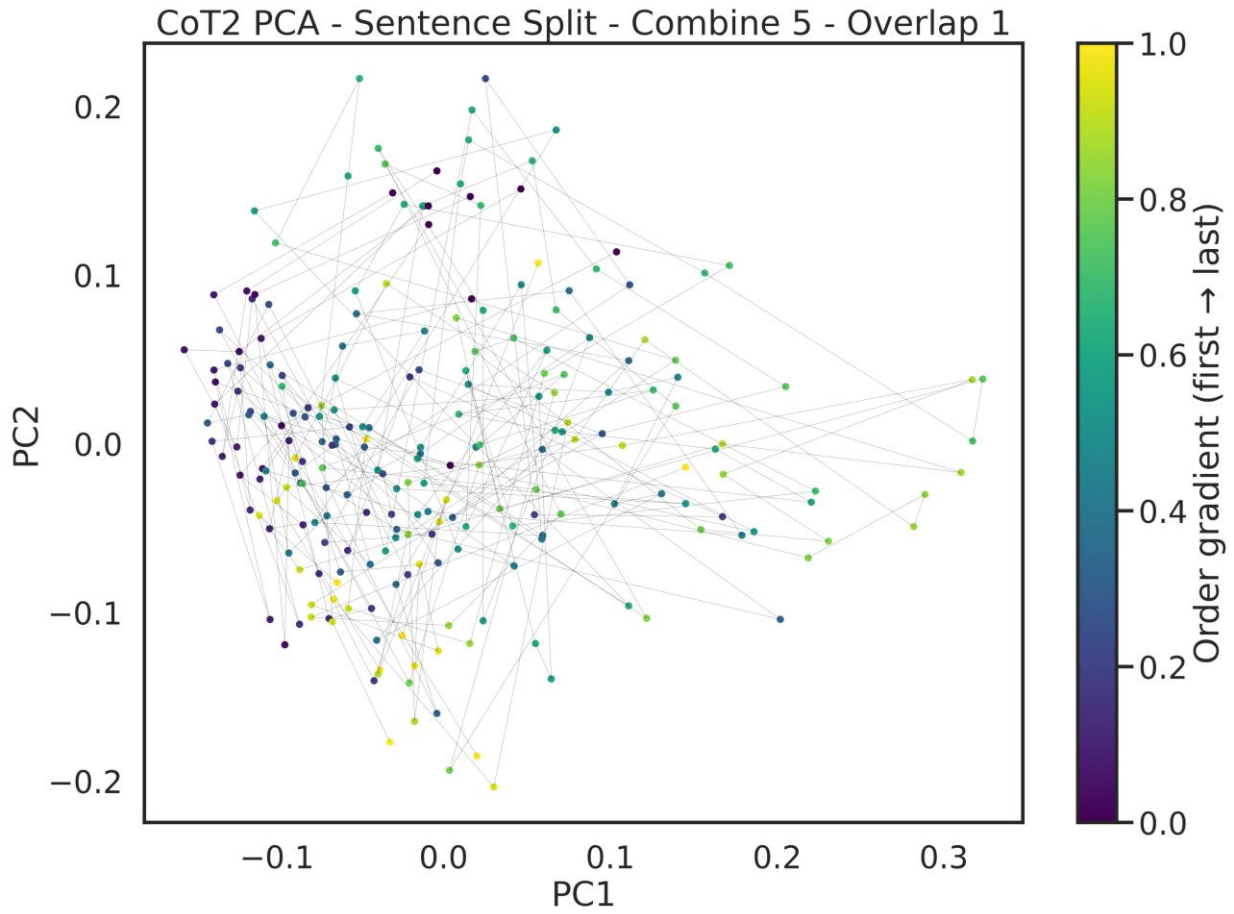
Which one is better? – Bold split, if goal is easy identification of outliers

CoT2

Less structured

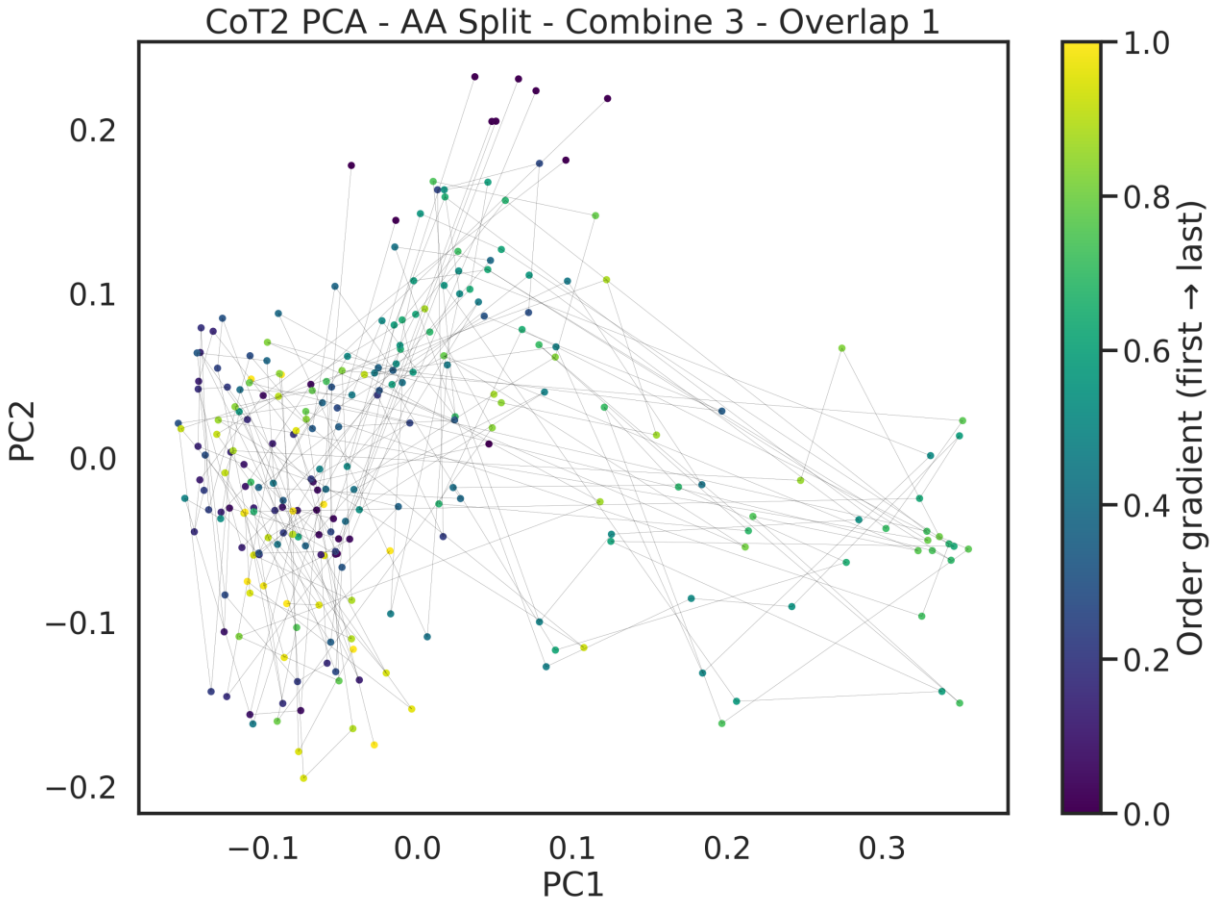
CoT2: Sentence Split

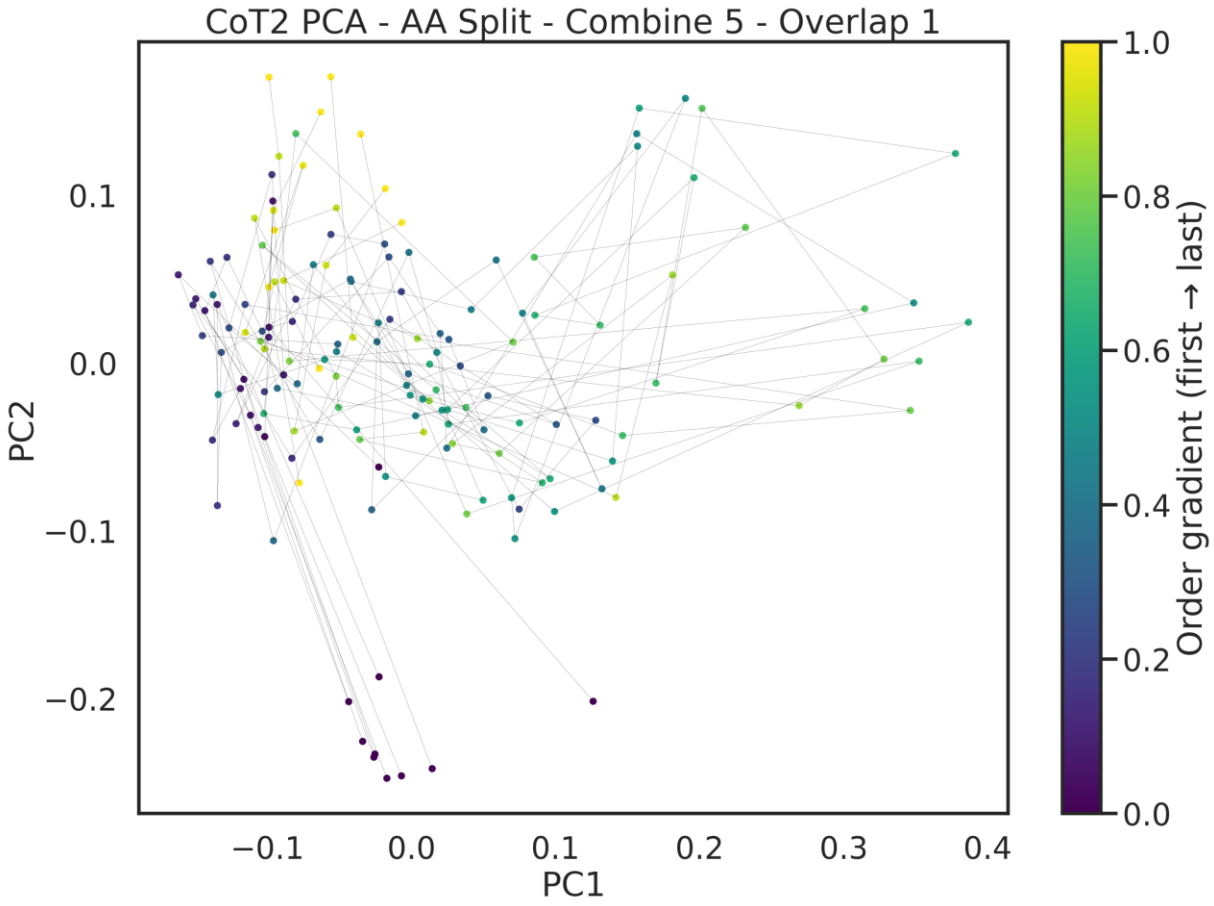




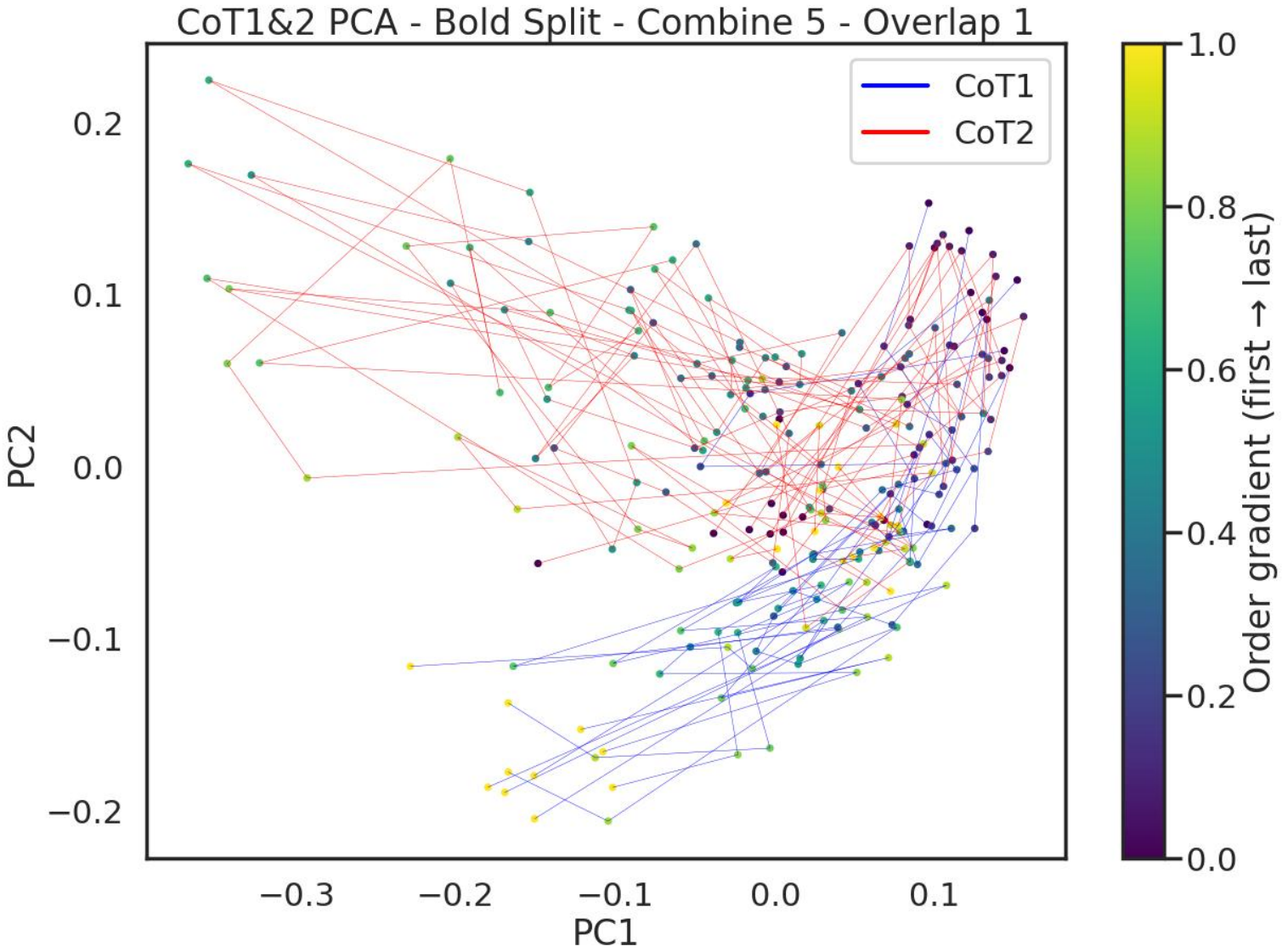
A lot more heterogeneity than CoT1

CoT2, Bold Split





Conclusion: CoT1 > CoT2



CoT2 seems to go in a completely different area of reasoning / logic / text

Modifying CoT2.0 → CoT2.1

```
[Final output should include only]
1.     The numeric Synergy Propensity Score (SPS)
2.     The categorical label
3.     A concise bullet rationale of mechanisms, biomarkers, and resistance factors
```

CoT 2.0

```
[Final output should include the thought process of the above steps, along with]
```

Cot 2.1

- More explaining / walk through together – “Let’s look at this together…”

```
cots/outputs$ grep -i "let's" cot1.*_output.txt | wc -l
0
cots/outputs$ grep -i "let's" cot2.1.*_output.txt | wc -l
44
```

- Introduces a lot of self-checks – is this a good thing?

SPS = tanh(-0.4495)
SPS ≈ -0.43

Interpretation: An SPS of -0.43 suggests an **antagonistic** or **additive/slightly antagonistic** effect based on this calculation. This indicates that the penalties (especially redundancy/bypass and seriality) are outweighing the potential synergistic drivers.

Revisiting the Logic - Focus on Direct Conflict:

The core issue might be that Actinomycin D *broadly* shuts down transcription. If a cancer cell is already *AR-dependent* and abiraterone effectively cripples AR signaling, the cell becomes highly reliant on other processes for survival. Actinomycin D, by broadly inhibiting RNA synthesis, would shut down *all* essential protein synthesis required for survival, including any remaining compensatory pathways. The previous calculation may have overemphasized penalties and underestimated the broad impact of Actinomycin D.

Let's reconsider:
Actinomycin D is a very potent cytotoxic agent that directly inhibits transcription. Abiraterone aims to starve AR-driven proliferation and survival.
If the cancer is *highly dependent* on AR signaling for proliferation and survival, then abiraterone's action is critical.
Actinomycin D, by broadly inhibiting transcription, will pr

CoT2.1.2

Consider a scenario where AR is downregulated by abiraterone, but the cell still has residual AR activity or relies on other pathways for survival. Actinomycin D would then kill the cell by inhibiting *all* transcriptional output needed for survival. This is more aligned with **parallel killing mechanisms** rather than strict synthetic lethality where one drug creates a vulnerability that the other exploits. However, the *context* highlights AR's role in activating proliferation and survival genes.

Let's think about resistance. If abiraterone resistance develops via AR amplification or mutations, Actinomycin D might still be effective by broadly inhibiting transcription. Conversely, if Actinomycin D resistance develops, the cell can survive.

Alternative Perspective - Synergistic Inhibition of Proliferation/Survival:

Let's re-evaluate the SPS with a focus on potent cytotoxic effects combined with pathway blockade.

Let's consider the *combination's effect on essential cellular outputs*. Abiraterone reduces the *signal* for proliferation/survival genes driven by AR. Actinomycin D prevents the *execution* of transcribing those genes (and all other essential genes). This combined blockade could lead to a more profound shutdown than either drug alone.

Revised SPS Calculation (Focus on potentiation of cell death):

Conclusion:

- Formula for success?
  - Bold Split, Combine 5, Overlap 1

Next Steps

- ModernBERT embedding model
  - – more nuanced. (currently intfloat/e5-base-v2)
- Different drugs
  - Double check trajectory
- Look into outliers from Bold Split, Combine 5, Overlap 1
  - Find semantic markers

Cosine Similarity (response-level)